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Third Report of the

Director of the National Heart and Lung Institute

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Annual report

NATIONAL HEART, BLOOD VESSEL, LUNG, AND BLOOD PROGRAM

Third Report of the Director of the National Heart and Lung Institute

December 29, 1975

National Heart and Lung Institute
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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND 20014

NATIONAL HEART AND LUNG INSTITUTE

December 29, 1975

The President
The White House
Washington, D. C.

Dear Mr. President:

I am pleased to submit to you for transmittal to the Congress, the third report on the National Heart, Blood Vessel, Lung, and Blood Program.

Cardiovascular diseases are responsible for more than half of all reported deaths. Coronary heart disease, the number one killer of the American people, continues as a primary focus of the National Program. However progress in its conquest is being made. Deaths from coronary heart disease, after increasing steadily for twenty-five years, have now shown a decrease for several years. In a like manner stroke and hypertension continue their downward trend. Despite these encouraging trends, more remains to be done in the conquest of cardiovascular, cardiopulmonary, and blood diseases. In addition to human suffering, these diseases cost the nation in sickness, lost wages, and benefits, an estimated $57 billion annually.

We have reported on the progress of the Program since the submission of the last Report. Utilizing the best scientific and professional judgement available, we have projected the resources necessary to accomplish program objectives within the time frame indicated. We recognize, however, that at any given time, allocation of national resources to execute the Institute's program must be determined in relationship to overall national needs.

Respectfully,

Robert Levy

Robert I. Levy, M.D.
Director

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I. Introduction

The National Heart, Blood Vessel, Lung, and Blood Act of 1972 expressed the determination of the President and the Congress to lessen the human suffering and financial burden caused by cardiovascular, pulmonary, and blood diseases and to improve utilization of national blood resources. The Act required the Director of the National Heart, Lung, and Blood Institute (NHLBI)* to expand, intensify, and coordinate the attack against these disease problems through development of a National Program and to submit an annual progress report to the President and the Congress.

The National Heart, Blood Vessel, Lung, and Blood Program Plan, and two previous annual reports of the NHLBI Director [1,2,3], covered in detail the status, accomplishments, and future short- and mid-term goals of the National Program, together with long-range objectives and planned actions directed toward their achievement. Legislative update of the 1972 Act in 1976 changes the reporting period from a calendar year to a fiscal year basis. Therefore, the current report has been prepared to cover the nine-month period from January 1, 1975, through September 30, 1975, thereby bringing subsequent annual reports into conformity with the new reporting requirements.

The initial Program Plan was formulated in 1973 and, since that time, as increasing knowledge opened new and fruitful avenues of endeavor, it has undergone continuous review, reassessment, and revision. The Program structure, during the period addressed by this report, is summarized in Table 1. It included ten program areas for heart and blood vessel diseases, eight for lung diseases, and four for blood diseases and blood resources.

The Program involves many interlocking relationships. The Institute, with the advice of the National Heart, Lung, and Blood Advisory Council,* other advisory committees, and the scientific community, has utilized its 27 years of accumulated expertise to create a many-faceted, well-integrated scientific effort to help relieve the American people of the sickness and heavy financial burden imposed by diseases of the heart, blood vessels, lungs, and blood.

Previous annual reports have described the overall development and expansion of the National Program, the evolution in organizational structure, and program management, as well as the means of communicating with both the health professional community and the public that NHLBI has implemented as a result of the expanded responsibilities mandated by the 1972 Act.

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* It is our understanding that pending amendments to the Public Health Service Act will change the name of the Institute to the National Heart, Lung, and Blood Institute and the name of its Advisory Council to the National Heart, Lung, and Blood Advisory Council.

TABLE 1.
NATIONAL HEART, BLOOD VESSEL, LUNG, AND BLOOD PROGRAM

HEART AND BLOOD VESSEL DISEASES	LUNG DISEASES *	BLOOD DISEASES AND BLOOD RESOURCES †
Arteriosclerosis	Structure and Function of the Lung	Bleeding and Clotting Disorders
Hypertension	Pediatric Pulmonary Diseases	Biomaterials
Cerebrovascular Disease	Emphysema and Chronic Bronchitis	Sickle Cell Disease and Related Disorders of the Red Blood Cell
Coronary Heart Disease	Fibrotic and Immunologic Lung Diseases	Blood Resources
Peripheral Vascular Diseases	Respiratory Failure	
Arrhythmias	Pulmonary Vascular Diseases	
Heart Failure and Shock	Inhalation Diseases	
Congenital and Rheumatic Heart Diseases	Respiratory Assistance	
Cardiomyopathies and Infections of the Heart		
Circulatory Assistance		

*Inhalation Diseases, which was a separate program area during the period covered by this report, will be incorporated into other relevant program areas in FY 1976. Similarly, Respiratory Assistance will be included as part of Respiratory Failure.

†Biomaterials, which was a separate program area in the Division of Blood Diseases and Resources during the period covered by this report, will be incorporated into the Circulatory Assistance Program of the Division of Heart and Vascular Diseases. In FY 1976, Disorders of the Red Blood Cell will be a separate program area.

Because of the brevity of this nine-month interim reporting period, it would be difficult, if not misleading, to attempt to supersede previous reports in all their ramifications and detail. Rather, this report focuses attention on new initiatives undertaken since passage of the 1972 Act. These include the Specialized Centers of Research, the Lipid Research Clinics, several major clinical trials, and the emerging National Research and Demonstration Centers Program. The combination of these targeted programs, together with a wide range of investigator-initiated research, has resulted in an effective National Program. The report also summarizes recent accomplishments in program coordination and gives examples of NHLBI's progress in prevention, control, and education activities related to the diseases falling under its mandate.

Chapter V discusses the Institute's manpower development programs. Chapter VI presents the NHLBI Resource Allocation Plan, which provides summaries of fiscal and staff allocations, together with a five-year projection of fiscal resource requirements needed to accomplish the National Program objectives.

II. Recent Accomplishments and Progress of the National Program

Heart, blood vessel, lung, and blood diseases have a devastating effect on the health of our citizens and on the nation's economy. More than 30 million Americans suffer from these diseases. In 1972 they led to an estimated national economic loss of more than $57 billion annually [4]. The above diseases constitute the most important public health problem facing the American people. In 1973, heart and vascular diseases were responsible for 53.8 percent of all reported deaths in the United States.

The Congress, recognizing the magnitude of the problem as well as the potential for advancement in the fight against these diseases, passed the National Heart, Blood Vessel, Lung, and Blood Act of 1972. This Act called for the development of a National Program. Four advisory panels and their task groups, drawn from universities, medical schools, hospitals, and other institutions nationwide, aided the National Heart, Lung, and Blood Institute in the formation of the National Program. Advice and recommendations were also sought from the National Heart, Lung, and Blood Advisory Council, the Interagency Technical Committee on Heart, Blood Vessel, Lung, and Blood Diseases and Blood Resources, and representatives of non-Federal and voluntary organizations with health-related interests and/or programs.

The Institute realizes that a continuing need of the highest priority is to develop the new knowledge which will enable us to better understand the fundamental processes involved in all diseases falling within the NHLBI mandate. Such knowledge is the prerequisite for prevention and rational treatment. No central authority can establish predetermined guidelines to obtain such knowledge. In the main it can only be developed by individual investigators, working in small or large groups, following their own leads, and pursuing problems of their own choosing. History bears out the importance of such basic non-directed research and our current level of knowledge and understanding has been provided, in large part, by the fruits of this non-directed research.

However, the distinction between basic and developmental research is seldom clearly understood by the general public and this has led to the misconception that systems analysis and "straight-line" research to a stated goal is all that is necessary for quick success. Therefore, when priorities must be set for limited funds and trained manpower, there is the tendency for targeted research to preempt broadly-based fundamental research for the allocation of these scarce resources.

This section of the report deals with some recent accomplishments within the National Program. However, accomplishments in biomedicine seldom are achieved rapidly or in isolation from other efforts and achievements in related research areas. Thus, definitive results reported today often represent the culmination of activities initiated many years previously. Each research accomplishment is but one piece of information in a large and growing

multidimensional mosaic. The investigator who makes the final "breakthrough" is acutely aware of the history of the problem he has been researching and of the past and current contributions of others towards its solution. Most successful research demonstrations have occurred only when the time has been ripe and the stage has been set. Even so, each piece of information that illuminates a problem reveals yet a deeper layer of questioning that needs to be undertaken.

HIGH BLOOD PRESSURE

. . . New Knowledge Offering Hope of New Treatments

Maintenance of a normal blood pressure is important to the health of an individual. The complex chemical control of blood pressure and the factors leading to abnormally high blood pressure are as yet incompletely understood. Recent studies in animals and in man have identified two additional substances which may be important in the control of normal blood pressure and which offer hope of new therapies for patients with high blood pressure. One of a series of events involved in blood pressure control is that an enzyme (biological catalyst) renin is released from the kidney into the bloodstream where it changes a plasma protein into a pressor agent, angiotensin I, which raises the blood pressure. Angiotensin I, in turn, is converted by another enzyme into a far more potent pressor agent, angiotensin II. Angiotensin II produces wide-spread constriction of the arteries, thereby raising the blood pressure. An inhibitor of the enzyme which converts angiotensin I into angiotensin II has now been developed and a second inhibitor has been developed against angiotensin II. Studies of these two inhibitors in animals and in man suggest that these substances are effective in the treatment of essential hypertension (by far the most common type of high blood pressure).

HEART DISEASE

. . . Relationship to Diabetes

The influence of diabetes mellitus on the evolution of cardiovascular disease was studied in a group of 5209 men and women aged 30 to 60 years who have been observed for 18 years in the Framingham study. A subgroup of 148 men and 153 women suffering from diabetes mellitus of sufficient severity to require insulin management was identified. This subgroup had at least a doubled incidence of cardiovascular disease and when such disease occurred, it was more likely to be fatal. Diabetes increased morbidity and mortality from all types of cardiovascular disease and the increase was more pronounced in women than in men. The lower incidence of cardiovascular disease found in normal women prior to menopause compared to the incidence in men of similar age was absent in diabetic women. In men, diabetes imposed twice the risk of congestive heart failure; in diabetic women, the incidence of congestive heart failure was threefold.

Risk factors for atherosclerotic disease such as elevated blood lipid levels, hypertension, and obesity were present more frequently in diabetics and the risk of cardiovascular disease associated with these factors was also

increased. Analysis of the epidemiological data reveals that when all other associated risk factors were taken into consideration, their presence could explain only 20 to 30 percent of the increase in cardiovascular disease risk found in diabetics.

HEART DISEASE

. . . Relationship to Risk Factors

Important new findings have been made which provide a more direct evaluation of the relationship between risk factors and the extent of coronary artery disease. Previous epidemiological data have related risk factors only to the clinical events of coronary heart disease, such as heart attacks. However, data from a recently completed special protocol autopsy study show direct correlation of risk factor levels during life with the subsequent extent of atherosclerotic lesions in the coronary arteries at autopsy. Prospective epidemiological studies in Puerto Rico found significant associations between the average percent of the inner surface of the arterial wall covered by raised atherosclerotic lesions and the preceding levels of serum cholesterol (a type of fat), blood glucose (sugar), and diastolic blood pressure.

HEART ATTACKS

. . . Studies in Women

New light is being shed on the incidence of heart attacks in women. Data on risk factors for coronary heart disease in women participating in the Framingham Heart Study (a group of individuals on whom epidemiological data have been gathered for over 20 years) show that serum cholesterol (a type of fat) increases abruptly following menopause. However, these investigations have also shown that this by itself does not account for the threefold increase in the incidence of cardiovascular disease found in these women in the postmenopausal years. The reasons for this increase in heart disease remain to be determined and studies are underway to gain more understanding in this area.

HEART ATTACKS

. . . Reducing Muscle Damage

In carefully selected patients, nitroglycerin, one of the oldest and best drugs for relief of the chest pain of angina pectoris, has now been shown by NHLBI scientists to reduce the extent and severity of heart muscle damage when administered soon after an acute heart attack. This confirms animal studies reported in the Second Annual Report of the Director. Limited clinical experience indicates that nitroglycerin alone reduces heart muscle damage in patients developing left heart failure in the wake of the attack. In patients without heart failure, the drug works best when used together

with phenylephrine, an agent that prevents the increased heart rate and drop in blood pressure that may occur in such patients when nitroglycerin alone is administered. Because the drug regimen required varies with the type of heart damage suffered by the patient, it must be carefully individualized for each case.

A second drug, hyaluronidase, when administered to dogs, reduces the extent of heart muscle damage following occlusion of the coronary artery. Recent preliminary studies in patients with acute myocardial infarction show that the hyaluronidase-treated patients exhibited fewer electrocardiographic and enzymatic signs of heart muscle damage than patients not receiving this drug.

HEART ATTACKS

. . . *Identification of a Significant Independent Risk Factor*

Collaborative epidemiological studies in Framingham, Massachusetts; Albany, New York; Honolulu, Hawaii; Claxton, Georgia; and in Israel have shown that low blood levels of alpha-lipoprotein cholesterol (a type of fat) are a significant independent risk factor for heart attacks. The high correlation of this relationship even in the 64- to 75-year age group provides a potentially important further refinement in the assessment of an individual's risk of having heart attacks. This additional blood lipid test should be useful both to predict coronary heart disease and to monitor intervention efforts against such disease. It is hoped that future prospective data from these studies will confirm this initial cross-sectional finding.

ATHEROSCLEROSIS

. . . *Studies of Blood Lipids*

Research interest in mechanisms of lipid (fat) transport in the body has intensified in recent years. Certain lipid transport disorders characterized by abnormal elevations of blood lipids have been identified as a major (in many patients the major) risk factor in the development of atherosclerosis and such lethal and crippling manifestations as heart attacks and strokes.

Several of the key advances in blood lipid studies pertain to a type of blood protein called apoproteins. These are natural "detergents" because they combine with fat soluble substances in the blood--cholesterol, triglycerides, and phospholipids--and convert them to water soluble complexes which can be readily transported in blood. Recently, scientists have determined the amino acid sequence of five of these apoproteins and identified the fragments of the dismembered apoprotein chain which combine with lipids. This has led to a new concept of the apoprotein molecule as a unique two-faced or amphipathic helical structure in which a large non-polar face binds the fatty acid chains of the phospholipids, and a second polar face combines with its water soluble portion. Synthesis of model apoprotein pieces has strengthened this hypothesis.

HIGH BLOOD LIPIDS (FATS)

. . . A Cellular Cause

The cellular defect which leads to elevated blood cholesterol in familial hypercholesterolemia (Type II hyperlipoproteinemia) has been demonstrated. Tissue culture experiments have shown that certain types of skin cells (fibroblasts) have specific receptors which bind and remove circulating low density lipoproteins from the blood. These receptors are either deficient or missing in cell cultures from patients with familial hypercholesterolemia.

ATHEROSCLEROSIS

. . . Portacaval Shunt Treatment in Patients with Familial Hypercholesterolemia

Familial hypercholesterolemia is a severely life-limiting genetic disorder in its homozygous form (both chromosomes carrying the defective gene), often resulting in advanced atherosclerosis and coronary heart disease in childhood or adolescence. The heterozygous disease (one chromosome carrying the defective gene), while less severe, is also accompanied by markedly premature atherosclerosis.

Treatment aimed at lowering the very elevated blood lipid levels of the rare homozygous form has had variable and limited success. The recent use in one such patient of an end-to-side portacaval shunt led to a marked decrease in hypercholesterolemia, a resorption of xanthomas, and an apparent regression of stenotic coronary artery lesions. These results, obtained in this single patient, suggest it is possible to reverse atherosclerotic disease in man by lowering highly elevated blood levels of low density lipids and cholesterol. This observation confirms in man the recently demonstrated regression of experimental atherosclerosis in rhesus monkeys brought about by feeding these primates low-cholesterol, low-fat diets. The implications for therapy of this initial observation are under study in several other patients. Further investigation of these results may also yield a better understanding of the determinants of lipid metabolism and atherogenesis.

ARTERY DISEASE

. . . Noninvasive Diagnosis

A new noninvasive diagnostic technique called phonoangiography has been developed. This method uses reflected ultrasound to provide a cross-sectional image in three dimensions of major blood vessels. The system can both detect and measure the degree of arteriosclerosis. In a clinical trial of 35 patients, atherosclerotic narrowing of the carotid arteries (which supply the brain) was measured both by this new noninvasive technique and by conventional invasive X-ray methods utilizing contrast media. Comparison of the results obtained by the two methods showed close agreement for all degrees of vessel narrowing.

The diameters of the stenotic arteries in these patients varied from 0.5 mm to 5.0 mm, with the standard deviation between the two series of measurements being ±0.46 mm.

Computer programs have been developed which enhance and quantify conventional femoral arteriograms (X-rays of the arteries supplying the legs) used for the diagnosis of disease in these arteries. A clinical prototype of a self-contained interactive computer image-processing system is being developed. This system can detect and display blood vessel edges, estimate the vessel midline and the diseased vessel lumen, and provide a numerical measure of the irregularity of the internal surface of diseased arteries.

SUDDEN CARDIAC DEATH

. . . Resuscitation of Victims

Well over 60 percent of the deaths from ischemic heart disease occur before hospitalization. And, in over 20 percent of patients, sudden death is the first and final manifestation of the disease. "Sudden cardiac death" need not be lethal. There are an increasing number of survivors because of improved out-of-hospital resuscitation. One highly successful program is the Seattle Heart Watch Program.

Ventricular fibrillation (a severe type of heart rhythm disturbance) is the predominant cause of sudden death. Significant progress has been achieved in successful resuscitation (defibrillation) of patients undergoing ventricular fibrillation. During the past four and one-half years, the Seattle Heart Watch Program, employing an upgraded emergency care system (using the existing fire-department ambulance system) has annually saved an average of a hundred lives in a community of one-half million.

Patient survival rates have increased steadily as experience in the delivery of pertinent, sound medical care was gained. During the first two years, approximately 11 percent of patients found in ventricular fibrillation by the rescue team survived the crisis. In the second two years, the survival rate improved to 25 percent, and it is still improving. Such emergency care is not practical in all localities, but if it could be delivered nationwide, it would save 40,000 or more lives annually.

HARMFUL EFFECTS OF CIGARETTE SMOKE

. . . New Evidence of Lung Damage

Chemical extracts of cigarette smoke have been shown to adversely affect the ability of the macrophages (cells responsible for clearing bacteria and debris from the lung) to perform their functions. Other chemical extracts have been shown to induce fibrosis or scarring in the lung. These studies add to the scientific basis for emphasizing the importance of smoking cessation programs.

HYPERSENSITIVITY PNEUMONITIS

. . . Isolation of a Causative Agent

Hypersensitivity pneumonitis, a lung disease resulting from the inhalation of certain organic dusts, significantly affects the gas transfer functions of the lung. In susceptible individuals, it occurs 4 to 6 hours after exposure to certain fine organic dusts and may persist for up to 12 hours. Although recovery is usually spontaneous after removal of the offending antigens, repeated exposure may result in irreversible pulmonary fibrosis. Antibodies against the offending antigen appear in the blood of affected patients as well as in a significant percentage of asymptomatic persons exposed to the same antigen. Therefore, the antibody reaction alone is not diagnostic of the disease. A causative agent has been isolated for one type of hypersensitivity pneumonitis (pigeon breeders' disease). This purified antigen (a basic glycoprotein) is now being used as a research tool to investigate the underlying mechanisms of hypersensitivity pneumonitis.

PROFOUND VENTILATORY INSUFFICIENCY

. . . Long-Term Respiratory Pacemaker Assistance

An implanted pacemaker to stimulate breathing has been used in thirty-three patients. These patients have been treated for profound ventilatory insufficiency by using a small diaphragm pacemaker implanted beneath the skin of the chest wall. Pacing is accomplished via an external antenna placed on the overlying skin which picks up a carefully programmed signal from a small external transmitter. Several patients have been symptom-free for at least six months following implantation of the pacemaker. Prior to the use of this device, they suffered repeated episodes of severe ventilatory insufficiency which required hospitalization.

EMPHYSEMA

. . . Possible Treatment

In normal individuals, the synthesis and breakdown of elastin, an important constituent of lung connective tissue, are in balance. Emphysema is associated with excessive breakdown of elastin by the enzyme elastase. Normally, elastase activity in turn is kept in check by other lung proteins or elastase inhibitors such as alpha-1-antitrypsin, which are deficient in some patients with emphysema. As a result of basic research on the structure and function of these naturally occurring elastase inhibitors, investigators have been able to synthesize synthetic inhibitors. The use of these synthetic inhibitors is being evaluated in animals. It may be possible to develop replacement therapy for those individuals deficient in inhibitors and so prevent emphysema in susceptible individuals.

LUNG GROWTH PROMOTING FACTOR

. . . Prevention of Hyaline Membrane Disease

A lung growth promoting factor has been isolated which may prevent development of hyaline membrane disease in infants born with immature lungs. An epidermal growth factor (EGF) has been isolated from human pregnancy urine. This peptide has growth stimulating activity and immunoreactivity similar to mouse EGF. Infusion of the human EGF into fetal lambs prevented respiratory distress syndrome (hyaline membrane disease) in lambs delivered prematurely. Also, the lungs of the treated animals were more mature structurally than those of their untreated control twins.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

. . . Early Detection

Early detection of potential chronic obstructive pulmonary disease may now be possible in asymptomatic individuals. Recent investigations have shown that measurement of closing volume combined with the maximal expiratory flow rate test can detect early pulmonary changes which can progress to chronic obstructive lung disease. Individuals with abnormal values for these tests, but normal values for other lung function tests, may be in an early phase of chronic pulmonary disease which, unlike the later symptomatic phases, is still reversible.

New techniques of determining the closing volume (the amount of air in the lungs after smaller airways collapse at the end of expiration) have been developed. Refined analysis of the closing volume curve and determination of the closing volume measured while breathing dense gas mixtures may increase the sensitivity of the method. These innovations are now undergoing clinical evaluation.

NEW OXYGENATOR DESIGNS

. . . Improved Materials

Extracorporeal oxygenation of blood is used clinically during cardiac surgery and respiratory crises. Recent developments have led to new designs in membrane oxygenators that are presently being evaluated in animals and in limited clinical settings. These design improvements involve the membrane material and its configuration. Materials development has produced several new substances that are now being incorporated into membrane oxygenators. These include microporous materials that result in significant increases in gas transfer rates as well as antithrombogenic coatings that produce marked reduction in the hematological damage produced by such devices. These advances are state-of-the-art improvements in our capability to provide extracorporeal oxygenation of blood for an extended time period.

OXYGEN THERAPY

. . . Oxygen Toxicity

Oxygen therapy is useful to patients with acute as well as chronic lung diseases. The use of high concentrations of inhaled oxygen is routine in the treatment of respiratory failure. Recent studies have shown, however, both symptomatic and pathologic changes in the human respiratory tract within days of continuous use of oxygen concentrations higher than 75 percent. Animals, as well as humans, develop tracheobronchitis and marked depression of mucus clearance. Further studies of the cellular aspects of oxygen toxicity have shown that damage to specific lung cell types may interfere with the healing of the lung. When used continuously for periods of months, concentrations of oxygen as low as 35 to 40 percent are capable of producing proliferation and engorgement of pulmonary capillaries. These findings have resulted in reassessment of the long-term clinical use of high concentrations of oxygen.

ANGIOTENSIN

. . . An Active Site for Metabolism

Investigators studying the conversion of angiotensin I to angiotensin II (important because of its role in blood pressure regulation as described above) have observed that a large fraction of this conversion takes place in the lung. Further work has identified the localization of this conversion site in the blood vessels of the lung circulation and has opened up new avenues for research into the role of the lung in metabolism of biologically active substances.

BASIC METABOLIC STUDIES

. . . Repair Processes in the Body

The basic metabolic research of NHLBI scientists and their colleagues in the National Cancer Institute (NCI) has led to the development of an important new source of human growth hormone. This hormone is important in tissue repair processes such as the repair of heart muscle damage after a heart attack. Until recently, human growth hormone was in very short supply. The very limited quantities of the hormone, extracted from the pituitary glands of human cadavers, were sufficient for therapeutic purposes only. However, the hormone can now be produced in significant amounts by human pituitary cells grown in test tubes in the laboratory. The growth hormone extracted from animal pituitary glands is inactive in man, and, to date, efforts to produce an active synthetic hormone have been unsuccessful. This new cell-culture technique has the potential to supply human growth hormone in quantities sufficient for both clinical and investigational purposes.

HEMOGLOBIN TYPING

. . . Prenatal Diagnosis of Blood Diseases

A micro-column chromatography procedure has been developed which can identify the hemoglobin type(s) of a single cell. Further refinement of this method will aid in prenatal identification of sickle cell disease. The method is also being field-tested for its ability to identify the carrier state of Cooley's Anemia.

HEMOPHILIA

. . . Improved Understanding

Recent research has indicated that most hemophiliacs have an abnormal form of antihemophilic factor (AHF) rather than an absolute deficiency. This abnormal AHF does not permit adequate blood clotting and normal AHF must be provided, usually as a concentrate, to prevent or control bleeding episodes. Detailed knowledge about the complex AHF molecule is increasing and a promising diagnostic scheme has been developed to detect carriers of hemophilia.

SURGERY

. . . Prevention of Thrombosis (Clotting of Blood in the Blood Vessels)

Certain patients, such as those undergoing many types of major surgical procedures, are particularly susceptible to postoperative thromboembolic complications. Approximately 25 percent of surgical patients develop venous thrombi detectable by sensitive techniques and 5,000 to 10,000 patients per year die of complicating pulmonary emboli (blood clots traveling to the lung). Low doses of heparin (5,000 units) given 2 hours preoperatively and every 12 hours after surgery until the patient is ambulatory have been found to prevent venous thrombosis, and perhaps pulmonary embolism. The use of heparin in this dosage preoperatively does not appear to lead to excessive bleeding during surgery.

III. Program Initiatives and Related Accomplishments

Different stages of knowledge and understanding exist for many of the diverse disease problems addressed by the National Program. For some diseases, basic underlying mechanisms must still be uncovered; others require the testing and evaluation of existing hypotheses as to successful treatment or cure. For a third group, the data exist for prevention, control, or cure, but this knowledge requires wide dissemination and application. Therefore, the program strategy employed by the National Heart, Lung, and Blood Institute for any individual disease consists of an ordered sequence of:

- Acquisition of new knowledge (basic and clinical research)
- Test and evaluation of promising hypotheses (clinical trials)
- Application of existing knowledge (education, demonstration, and control).

Progress is being made in each area of the overall strategy. Creative research by individual investigators and by teams of investigators is leading to new knowledge about heart, blood vessel, lung, and blood diseases. Targeted research is being supported to attack problems urgently requiring solution in those situations where the underlying data base exists to make such research feasible. And, imaginative new approaches are being initiated to decrease the time needed for the translation of this new knowledge into improved health care.

The overall reduction in deaths from cardiovascular disease depicted in Table 2 is an encouraging sign that the previous years of Federal support for NHLBI research and development efforts against these diseases are being translated into an increase in life-expectancy. Over the last five years, deaths from the number one killer of the American people--coronary heart disease--after years of increase, have shown a slight decline resulting in a saving of the lives of approximately 14,000 Americans a year.

The Institute has sought to maximize this progress by supporting vigorous nondirected, investigator-initiated research supplemented by a program of more targeted research. This chapter reviews some of these targeted programs, including the Specialized Centers of Research; the National Research and Demonstration Centers; the Lipid Research Clinics Program; large-scale clinical trials; and prevention, control, and education programs. Programs are underway to develop better, more sensitive, noninvasive techniques to

TABLE 2.
TREND IN AGE-ADJUSTED DEATH RATES ATTRIBUTED TO CARDIOVASCULAR DISEASES 1940 TO 1973*

DISEASE	AGE-ADJUSTED DEATH RATES PER 100,000 POPULATION						
	1940	1950	1960	1965†	1968†	1970	1973
Total Cardiovascular Disease	507.8	440.1	396.9	378.4	368.4	346.3	333.2
Coronary Heart Disease	207.2	226.4	238.5	237.2	241.6	228.1	218.9
Stroke	105.0	88.8	79.9	73.3	71.3	66.3	63.7
Hypertension	69.3	56.0	29.6	22.4	9.5	7.9	6.3
Rheumatic Heart Disease	20.5	14.0	9.7	7.5	7.2	6.3	5.4
Other Cardiovascular Disease	105.8	54.9	39.2	38.0	38.8	37.7	38.9

DISEASE	PERCENTAGE CHANGES IN AGE-ADJUSTED DEATH RATES					
	1940-1950	1950-1960	1960-1965	1965-1968‡	1968-1970	1970-1973
Total Cardiovascular Disease	-13.3	-9.8	-4.7	NA	-6.0	-3.8
Coronary Heart Disease	+9.3	+5.3	-0.3	NA	-5.6	-4.0
Stroke	-15.4	-10.0	-8.3	NA	-7.0	-4.0
Hypertension	-19.2	-47.1	-24.3	NA	-16.8	-20.3
Rheumatic Heart Disease	-31.7	-30.7	-22.7	NA	-12.5	-14.3
Other Cardiovascular Disease	-48.1	-28.6	-3.1	NA	-2.8	+3.2

*Source: National Center for Health Statistics.

†Data prior to 1968 cannot be directly compared with later data because of changes in the International Classification of Diseases.

‡Trend data not available because of changes in the International Classification of Diseases.

diagnose heart, blood vessel, lung, and blood diseases and to produce reliable standardized animal models of these diseases. NHLBI has also undertaken an expanded schedule of seminars, workshops, and conferences designed to increase the exchange of information and facilitate interdisciplinary people-to-people contacts so important in stimulating new approaches and creating better understanding in science and medicine.

SPECIALIZED CENTERS OF RESEARCH (SCORs)

In 1971, the NHLBI, on the recommendation of its Advisory Council, initiated its first series of Specialized Centers of Research. The initial program consisted of four groups of SCORs, each group addressing one of the following disease areas: arteriosclerosis, hypertension, pulmonary diseases, and thrombosis. Since the initiation of the National Program, these SCOR programs have expanded and developed into a highly successful enterprise. In FY 1975, a

fifth group of SCORs, focusing on coronary or ischemic heart disease, was added to this program.

A SCOR is an identifiable organizational unit within its institution with a central theme to which all individual projects relate. The specific purpose of these grant-supported centers is to advance basic knowledge and develop the most effective methods of clinical management and prevention in their designated disease areas. Programs of a SCOR may include basic, developmental, or applied projects and clinical investigations. The SCOR concept requires that each type of SCOR be a part of a national network of Centers of Research addressing similar problem areas and that there be close coordination among SCORs within the network. To accomplish this active coordination, SCOR Directors meet regularly to review progress, discuss common interests and problems, and plan collaborative efforts. Each SCOR also has a special collaborative relationship with the NHLBI, working closely with the Institute staff to further appropriate NHLBI goals as set forth in the National Plan.

The interaction of scientists from various disciplines within a SCOR is more than a casual one brought about by mutual interests in the designated SCOR research area. There is an active collaboration of basic scientists and clinical researchers on projects of mutual interest. In addition, SCOR investigators are made aware of the entire SCOR program via seminars in which they describe their own current research activities and learn of relevant work by other investigators.

Although the usual award period for a SCOR is five years, continuation of support is subject to satisfactory performance. Evaluation of each SCOR is carried out via periodic visits of Institute staff and outside consultants to review progress. In addition, scientific progress is evaluated annually by members of the appropriate NHLBI Scientific Advisory Committee. This peer review by non-Institute scientists is an important component of the evaluation of each SCOR.

Half a decade of experience with the SCOR program has demonstrated its value for highly original basic research, for scientific communication, and for applied research in preventive and therapeutic medicine. The new competitive solicitations, now underway or recently completed for additional SCORs, should further invigorate this program.

Arteriosclerosis SCORs. The Institute is supporting 13 Arteriosclerosis SCORs. The programmatic focus is on the development and application of new knowledge essential for the improved diagnosis, treatment, and prevention of atherosclerotic disease. Current activity centers on three major programmatic areas with each area containing several different types of studies. One programmatic area involves clinical studies of hyperlipidemia and/or vascular disease which include:

- Characterization and biochemical-genetic disease relationships

- Control by diet and drugs
- Development of diagnostic instrumentation for assessment of lesions
- Adult coronary heart disease risk factor population studies, trials, and interventions
- Adult coronary heart disease risk factor reduction via lifestyle modification
- Prevalence studies among 14,000 children from four different SCOR populations of risk factors such as diabetes, high blood pressure, and high blood lipids.

Animal and tissue studies of atherosclerosis comprise a second area and include:

- Experimental atherosclerosis (non-human primates, other mammals, and non-mammalian species)
- Diet and drug effects on lesion progression/ regression
- Parameters of atherogenesis in arterial wall and tissues
- Cell culture and lipid-lipoprotein metabolism
- Relationships of hypertension, diabetes, and cigarette smoking to arteriosclerosis.

The third major programmatic area is devoted to basic laboratory investigations and includes:

- Characterization of lipoproteins, apoproteins, and their interactions with lipids
- Metabolism of lipoproteins and lipids
- Vascular thrombosis and intravascular coagulation, as these affect arteriosclerosis.

A second national competition for Arteriosclerosis SCORs was announced in May 1975. Renewal of current SCOR grants and the addition of new Centers are under competitive review. Funding of the approved applications is expected to begin in December 1976.

Hypertension SCORs. A thorough understanding of the etiology and pathogenesis of hypertension is needed for its effective treatment and prevention. The objective of the five Hypertension SCORs is to expedite the development and application of new knowledge essential for improved diagnosis, treatment, and prevention of all types of hypertension, including its primary and secondary forms. The Hypertension SCORs are studying particular clinical problems which include:

- Relative value of surgical versus medical treatment of renovascular hypertension
- Development of new therapeutic regimens for the treatment of hypertension, including the use of propranolol, minoxidil, and the converting enzyme inhibitor SQ20,881
- Management of severe or malignant hypertension with kidney involvement
- Development of improved methods to measure renin, aldosterone, and catecholamines
- Behavioral and genetic factors in hypertension
- Renin-angiotensin-aldosterone system in essential and secondary hypertension
- Effective drug treatment as a function of plasma renin
- Mechanisms involved in maintaining fluid and electrolyte balance under normotensive and hypertensive conditions
- Determination of humoral factors in the pathogenesis of hypertension in animal models as well as in hypertensive patients
- Genetic studies in twins aimed at separating genetic and environmental factors which contribute to hypertension.

A second national competition for Hypertension SCORs was initiated in June 1974. Renewal of current SCOR grants and the addition of new Centers were considered. Renewal of three of the five original SCORs and the establishment of one new SCOR were approved by the National Heart, Lung, and Blood Advisory Council in June 1975. Funding will begin in December 1975.

Ischemic Heart Disease SCORs. From 1967 to 1974, the Myocardial Infarction Research Units (MIRUs) undertook a program of clinical and basic research directly related to heart attack (one manifestation of coronary or ischemic heart disease) in man. These were replaced in FY 1975 by nine Ischemic Heart Disease SCORs. These new centers are more broadly focused than the MIRUs and include other manifestations of ischemic heart disease. Their aim is to reduce the death rate and disability from this disease. Current programs include:

- Research on early detection of latent ischemic heart disease and electrophysiological responses to cardiac ischemia
- Evaluation of acute and chronic antiarrhythmic therapies
- Studies of coronary artery bypass graft surgery
- Research on agents which provide additional nutrients or decrease myocardial oxygen demands and so protect ischemic heart muscle
- Development of optimal cardiac resuscitation techniques
- Development of invasive and noninvasive techniques to detect coronary arteriosclerosis
- Studies on the causes and prevention of sudden cardiac death including premonitory signs and metabolic and electrophysiological risk factors
- Development of improved methods for the psychological and physical rehabilitation of patients recovering from an acute heart attack
- Precordial mapping of electrocardiograms and automated arrhythmia analyses.

Pulmonary SCORs. Seventeen Pulmonary SCORs are being supported by the Institute. They are concerned with basic and clinical research on various aspects of pulmonary disease. Individual SCORs address their research to one or more disease categories. Over the last few years, research into pulmonary disease has increased and the interdisciplinary approaches that characterize the SCOR grant are now emphasized in several of the areas in the National Program Plan. A new open competition for Pulmonary SCORs was announced in May 1975. The new Pulmonary SCORs (to be funded in December 1976) will address one of four disease categories requiring further emphasis; namely, chronic diseases of airways, pediatric pulmonary diseases, fibrotic and immunologic pulmonary diseases, and pulmonary vascular diseases. Each new SCOR may address itself only to a single disease category. Within these disease categories, topics of particular interest are:

- Irreversible chronic bronchitis and emphysema

- Asthma
- Hyaline membrane disease (neonatal respiratory distress syndrome)
- Cystic fibrosis
- Bronchiolitis and other obstructive lung diseases
- Identification of risk factors for fibrotic and immunologic pulmonary diseases
- Pulmonary hypertension and cor pulmonale
- Pulmonary edema.

Thrombosis SCORs. The Institute supports five Thrombosis SCORs to focus resources, facilities, and manpower on the improvement of diagnosis, treatment, and prevention of thrombosis. The program is concerned with the elucidation of the pathogenesis of thrombi and the study of promising observations and interventions. Studies in these SCORs include work on:

- Identification of individuals susceptible to thrombosis and evaluation of preventive therapy
- Development of methods for detection of incipient hypercoagulability and covert thrombosis
- Development of laboratory techniques for the evaluation and control of thrombosis therapy
- Study of chemicals potentially able to prevent thrombosis or to lyse thrombi already formed
- Noninvasive techniques to detect deep vein thrombosis
- Study of cellular, chemical, and hemodynamic variables in the production of thrombi
- Biochemical basis for antithrombotic therapy
- Role of endothelium in the initiation of thrombosis and in fibrinolysis, including interactions between the endothelial surface and blood proteins
- Role of platelets in microcirculatory pathology

- Relationship of thrombosis to arteriosclerosis, including the distribution of thromboplastic activity and fibrinolytic activity in the vessel wall and the role of fibrinolysis in the pathogenesis of arterial disease

- Relationship of vascular injury to platelet aggregation and fibrin formation and the role of endothelial damage in early thrombogenesis

- Risk factors associated with venous thrombosis, including the identification of the thrombosis-prone individual and the elucidation of the "hypercoagulable state"

- Development of diagnostic instruments of a chemical, physical, or physiological nature that would markedly enhance the sensitivity and specificity for detecting clinically "silent" thrombotic lesions

- Clinical trials of platelet-inhibiting drugs for prevention of thrombosis in patients at high risk

- Role of hormones and their influence on vessel walls and thrombosis.

A new national competition for Thrombosis SCORs was initiated in December 1974. Competitive renewal of current SCOR grants and the addition of new centers are being considered. Funding of approved applications is expected to begin in January 1976.

THE LIPID RESEARCH CLINICS (LRC)

The Institute supports 11 Lipid Research Clinics in the United States, one in Canada, and one in Israel. Two additional LRC Clinics, supported by the Soviet Union, are located in the USSR. These Clinics conduct a broad, collaborative research program on the structure, metabolism, and function of lipids and lipoproteins as they relate to atherosclerosis. In addition, they support a program of research on the diagnosis and management of hyperlipoproteinemia. They were established in 1971 and 1972 as an outgrowth of the active research program on blood lipids and their abnormalities in which NHLBI scientists had been engaged for over ten years.

A major activity within the Lipid Research Clinics Program is a primary prevention trial to test whether reduction of blood cholesterol will reduce heart attacks in a group of hyperlipidemic patients. The trial is described in the section on clinical trials. In addition, the LRC Program encompasses several collaborative studies and support groups listed below:

- Core laboratories have developed standardized definitions for the hyperlipoproteinemias, current

criteria for their diagnosis, and standardized techniques to determine lipids and lipoproteins.

- Epidemiological studies are determining the frequency and natural history of the various dislipoproteinemias (blood fat disorders) and their relationships to coronary heart disease risk factors.

- Genetic studies are underway to determine the quantitative effects and the interrelationships of hereditary factors as compared to environmental ones in lipid disorders. The modes of inheritance and penetrance of lipoprotein abnormalities are also being investigated.

- Nutrition programs include development and implementation of dietary therapy for the trials, the development of a standardized methodology to collect nutritional data, dietary counseling methods and motivational tools, and consultative services for professional and lay communities on the relationship of diet and hyperlipidemias.

- Basic science research programs are utilizing LRC facilities and staff resources to promote concurrent basic and clinical investigations on the hyperlipoproteinemias.

- Education of local community physicians on the detection, diagnosis, and improved management of hyperlipidemic patients is being carried out.

Through the US-USSR Cooperative Health Exchange Program, the Lipid Research Clinic prevalence studies of the hyperlipidemias and ischemic heart disease have been expanded into an international study. The Soviet lipid research clinics are located in Moscow and Leningrad. This collaborative study is discussed in more detail in Chapter IV. The recent establishment of a clinic in Jerusalem, Israel, further increases the international scope of the LRC Program. It will enable prevalence studies to be carried out in a multi-ethnic population.

Some of the recent accomplishments and future plans of the Lipid Research Clinics are summarized briefly below:

- All core lipid laboratories have achieved and maintained satisfactory standardization of laboratory methods.

- An extensive standardization program has been established for the prevalence studies. Approximately 57,000 first visits and 12,000 second visits have been recorded.

- Standardized nutrition data collection procedures have been developed in coordination with the Multiple Risk Factor Intervention Trial program (MRFIT) described elsewhere in this chapter. Other recent joint accomplishments in the area of nutrition are summarized in Chapter IV.

- Inexpensive accurate methods to determine levels of blood cholesterol, triglycerides, and lipoprotein have been developed in cooperation with industry. A manual describing these techniques [5] is being widely used in clinical chemistry laboratories.

- Preliminary planning of a low-cost mortality surveillance study of subjects in the prevalence studies has begun. This study hopes to determine if triglycerides and plasma lipoproteins are independent risk factors for coronary artery disease.

NATIONAL RESEARCH AND DEMONSTRATION CENTERS (NRDC)

Public Law 92-423 states that the Director of the Institute may provide for the development of National Research and Demonstration Centers: up to 15 Centers for problems related to heart, blood vessel, and blood diseases; and up to 15 Centers for problems related to chronic lung diseases. The purpose of the Centers program is to facilitate and expedite the translation of basic research findings to practical patient care in local communities across the nation. The act specifies that this program would encompass "... basic and clinical research into, training in, and demonstration of, advanced diagnostic, prevention, and treatment methods ..." for the respective diseases. The NRDC was envisioned as a national resource attached to a major medical complex and dedicated to working in close collaboration with the NHLBI to further the goals of the National Program. The Act authorized 30 Centers costing up to $5 million each; however, because of funding constraints, the Institute has been able to establish only three such Centers, one for each of the categorical areas.

The program of the three established Centers encompasses the whole spectrum of health activities--from basic and clinical research, through training and education, to demonstration of diagnostic, prevention, and treatment methods. It is the inclusion of education and demonstration components and the coordination of these programs with the research and training efforts of the Center that is the special feature of this program. The mission of the NRDC is not to be a direct service facility for the local community, nor is it a means of funding primary health care. A major function is to investigate how best to translate the latest research advances rapidly into improved medical care and, through demonstration programs, to disseminate these new treatment modalities as widely as possible. The NRDCs represent national, or regional, as well as local resources.

The presence in the Center of scientists and other professional personnel representing many disciplines creates an environment in which the participants interact in effective and productive ways. In particular, the interaction of scientists and practitioners of various health science specialities expedites the solution of the categorical disease problems addressed by the Centers. This multidisciplinary milieu also provides a setting conducive to the training of young scientists.

Built into the activities of each of the Centers is a prospective evaluation plan. This plan will be used to assess the impact and effectiveness of the Center concept. Each Center has tailored this plan to its specific needs. However, all plans call for several review groups, consisting of a mix of Center staff and ad hoc consultants. During the process of formulating the type and scope of each Center's projects, a strong working partnership has been developed between the Institute staff and the staff of the NRDCs.

National Research and Demonstration Center (Cardiovascular Diseases). The program of the National Research and Demonstration Center at the Baylor College of Medicine in Houston focuses on heart and blood vessel diseases, particularly arteriosclerosis. Ongoing or planned research projects to be undertaken by this center include investigations of:

- The structure, function, and metabolism of lipoproteins
- The morphology of arteriosclerosis; the distribution of arteriosclerotic deposits in the arterial system; the relationship between blood-lipid profiles; the development of arteriosclerotic deposits; and the lipid composition of these deposits
- The physiology of heart muscle and the causes, effects, and therapy of coronary-artery and heart-muscle disease
- The surgical management of heart and blood vessel disease, including removal or bypass of arterial obstructions; the development and evaluation of mechanical devices to provide pumping assistance to heavily damaged or failing hearts
- Immunological factors that may operate in the development of arteriosclerosis or else may be activated by the disease process
- Blood resources and the problem of hepatitis, particularly as they relate to open-heart surgery.

Control and demonstration projects include:

- Application to community clinics and hospitals of preventive treatment and rehabilitative procedures as practiced in the Baylor Cardiovascular Center
- Employment of special ambulances equipped with telemetering equipment, permitting physicians in participating hospitals to monitor the clinical status of heart attack victims or other cardiovascular emergencies and to supervise their treatment while the patient is enroute to the hospital
- Alteration of risk factors strongly associated with increased susceptibility to coronary heart disease and its complications, such as acute heart attacks; in particular, the elimination or reduction of cigarette smoking and the modification of habitual dietary patterns (diets high in calories, total fats, and cholesterol) that tend to raise blood lipid levels.

National Research and Demonstration Center (Pulmonary Diseases).
The National Research and Demonstration Center at the University of Vermont in Burlington concentrates on lung diseases, with special emphasis on occupational pulmonary disease resulting from prolonged exposure to harmful dust and fumes in various industries and occupations. Ongoing or planned research programs of the Vermont Center include investigations of:

- Occupational lung diseases such as silicosis and farmer's lung, emphasizing epidemiology, prevention, and control in defined population groups; the potential causes of dust-inhalation diseases and their effects on lung architecture and lung function
- Epidemiology of sub-clinical lung diseases which may produce few symptoms early in their course, but which may impair respiratory function and result in serious illness later on
- Cellular functions in the lung; the operation of cleansing mechanisms in the lung after exposure to dust and fumes; the origins, mechanisms, and consequences of diffuse fibrosis of the lung
- The pathology and clinical management of trauma to the respiratory system; intensive care of pulmonary trauma victims.

Demonstration projects include:

- Development of a state-wide network for surveillance, diagnosis, treatment, and control of tuberculosis, industry-related lung diseases, and other pulmonary disorders in ambulatory patients

- A program for providing regional assistance in the management of respiratory diseases, employing an inter-hospital computer network for information storage and retrieval, data interpretation and analysis, aids in diagnosis and treatment, and the dissemination of new knowledge

- Development of a computerized progressive care program, oriented to clinical problems of respiratory diseases, that will draw on and integrate the developing methodology and technology, provide technical assistance and quality control in clinical care, and evaluate the results of new programs within community hospitals

- Dissemination of new knowledge via a television network linking seven medical care facilities and two university medical centers

- Development of a patient education program employing self-instruction and audio-visual techniques to help patients understand the nature of their disease and so encourage their full cooperation in treatment and control measures

- Development of a regional public information system on respiratory diseases in collaboration with the Vermont Lung Association and the State Health Department.

National Research and Demonstration Center (Blood Resources). The National Research and Demonstration Center at the Puget Sound Blood Center in Seattle is mainly concerned with improvement of procedures for the acquisition, processing, storage, distribution, and clinical use of blood and blood products. Ongoing or planned research projects undertaken by the Center include:

- Preparation and characterization of blood clotting factors, particularly antihemophilic factors (AHF or Factor VIII) and Christmas Factor (Factor IX)

- Preparation and evaluation of highly purified bovine Factor VIII for potential use in hemophiliacs with circulating antibodies against human Factor VIII

- Development of improved methods to preserve blood platelets and to detect and cope with platelet antibodies that reduce the effectiveness of platelet transfusion in some patients

- Studies to improve the effectiveness of massive transfusions in patients who have sustained heavy blood loss through accidents, major surgery, etc.

- Studies of white cell transfusions as a possible way to prevent potentially lethal infections in patients with very low white-cell counts.

Demonstration projects include the following aspects of blood banking:

- Increasing community blood resources through development of effective education and recruitment programs for volunteer blood donors

- Assisting hospitals and clinics to make optimal use of available blood resources, encouraging use of the specific blood component required by the clinical situation, such as packed red cells, platelets or plasma fractions, rather than the "scatter-gun" approach of transfusing whole blood

- Providing training and education programs for laboratory technicians, medical students, hematology trainees, and physicians within the community.

MAJOR CLINICAL TRIALS

" ... The proper study of mankind is Man."
Alexander Pope (1686-1744)

The essential final test of the effectiveness of promising research findings and clinical hypotheses is a controlled clinical trial in man. Large-scale controlled trials require the close collaboration of clinical investigators in many institutions nationwide, for no single institution possesses the necessary physical resources, professional skills, or patient population. To obtain comparable results, participating institutions in a trial must adhere strictly to the detailed protocol developed for the trial. And, because end points are usually statistical changes in the occurrence of increased morbidity or mortality from a chronic disease, these trials may require years to obtain definitive results.

The clinical trials described below are both complex and expensive. They involve many investigators in a large number of medical centers and they require

long-term commitment of a considerable portion of the Institute's budget for successful completion. Given limited resources, the Institute must continually evaluate the cost-effectiveness of on-going trials and it must consider even more carefully any additional commitment to new trials that may be occasioned by new research hypotheses requiring definitive testing in man.

Coronary Drug Project (CDP). This five-year nationwide trial of 8,431 male coronary patients was begun during the 1960s on the recommendation of the NHLBI Advisory Council. Fifty-three clinics participated in the CDP. Its clinical phase was completed in January 1975. The purpose of the study was to test whether drugs that lower certain blood lipids (cholesterol and triglycerides) confer protection against recurrent heart attacks or improve long-term survival among men aged 30 to 60 years who had suffered one or more clinically confirmed heart attacks. Patients receiving one of five medically promising drug regimens were compared with a control group receiving standard medical treatment plus placebo. All participants were under study at least five years.

Three treatment regimens (high and low estrogen and dextrothyroxine) were discontinued early in the study because they displayed adverse effects without increasing survival rates. Patients in the high estrogen group had more serious, non-fatal cardiovascular events than the controls, the low estrogen group had an increased risk of thromboembolism, and dextrothyroxine decreased survival rates, particularly among higher risk patients. Evaluation of the two remaining regimens, clofibrate and nicotinic acid, was continued for at least five years. They lowered blood lipids somewhat, but they did not appreciably improve survival rates. Moreover, they too were associated with an increase in non-fatal cardiovascular events as well as other serious side effects.

The Coronary Drug Project, by using standardized methodologies, demonstrated unfavorable features of several drugs once considered beneficial for patients already suffering from coronary heart disease. It did, however, illustrate that the placebo control group of a clinical trial is not necessarily denied a useful form of therapy. On the contrary, this group fared as well, or better than, any treatment group. Thus, this trial underscores the value of large-scale, well-controlled clinical testing of regimens, the safety and efficacy of which are assumed solely on the basis of limited clinical testing. The results of the CDP have been published in the scientific literature. They are also being actively communicated to the medical community through other media.

Although the CDP cost $41.5 million, this is considerably less than the estimated $75 million spent annually in America alone on clofibrate. The proportion of patients for whom the drug is prescribed to prevent a first heart attack, as distinct from a second heart attack, is unknown. It should be noted that the results of the CDP provide no insight into whether lipid lowering therapy is effective in preventing first heart attacks in patients at high risk.

The study produced a very large body of valuable data on the natural history of acute heart attack. It showed that the mortality rate following a heart attack can be predicted on the basis of 11 clinical and electrocardiographic findings. Use of this information will improve the future long-term management of persons recovering from such an attack.

Multiple Risk Factor Intervention Trials (MRFIT). The Multiple Risk Factor Intervention Trial, a six-year clinical trial undertaken on the advice of the Arteriosclerosis Task Force [6], was begun in 1972. Aimed at our most important contemporary health problem, coronary heart disease, it is the largest and most difficult primary prevention trial ever undertaken by NHLBI. Its goal is to prevent first heart attacks among men aged 35 to 57 years in the upper decile of the distribution of risk of death from coronary heart disease due to a combination of elevated serum cholesterol, elevated blood pressure, and cigarette smoking. Participants must have no pre-existing clinical coronary heart disease. Half of those selected are being randomly allocated to a special intervention program and half are being referred to their usual source of medical care. The MRFIT trial involves 20 clinical centers across the country with a total of 12,000 participants. Each of the centers will screen from 12,000 to 20,000 candidates so as to identify and enroll its share of the needed 12,000 eligible participants. Over 200,000 men have been screened and over 8,000 participants have been enrolled to mid-1975. The primary recruitment phase of the study is expected to be completed by January 1976.

The intervention program consists of simultaneous dietary modification to lower blood lipids, drug therapy for high blood pressure, and counseling to discontinue or reduce smoking. The program is designed to achieve and maintain a 10 percent reduction in serum cholesterol, a 10 percent reduction in diastolic blood pressure, and a 20, 30, and 40 percent reduction in the number of cigarettes smoked by heavy, moderate, and light smokers, respectively. The effect of the special intervention program on the incidence of coronary heart disease (both non-fatal and fatal heart attacks), cardiovascular mortality, and total mortality from all causes will be monitored and the results analyzed.

A nutrition data collection program has been established which has standardized nutrition data collection procedures and training and certification of personnel at each clinic. Improved techniques of group education and individual instruction are being applied to produce changes in dietary patterns. New educational materials are being developed in coordination with the Lipid Research Clinic Program (LRC), which are of potential value for application to the community. Recent collaborative accomplishments in the area of nutrition are summarized in Chapter IV.

This trial will also greatly enhance our knowledge of effective methods for controlling major risk factors in free-living, subjectively healthy, coronary-prone, middle-aged American men and how to change the living habits of these men and their immediate families.

Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT). This trial, commenced in 1973 on the recommendation of the Arteriosclerosis Task Force [6], is a seven-year study to test whether lowering cholesterol in hypercholesterolemic otherwise healthy subjects will reduce or slow the development of premature coronary heart disease.

Investigators have identified distinct lipid transport abnormalities. Each differs in its clinical manifestations, risk of producing secondary disorders, and responsiveness to therapy. The increased blood lipids associated

with these disorders may often be lowered by specific therapeutic diets with or without lipid-lowering drugs.

One of the most common of the blood lipid disorders, Type II hyperlipoproteinemia, is being studied in this trial. It is one of the most dangerous of the lipid disorders because of the associated high risk of premature atherosclerosis. Patients with this disorder are at high risk of death from coronary heart disease at a rate 2.5 to more than 10 times that of normals. Heart attacks in men under 50 with the Type II disorder are common.

Twelve lipid clinics, eleven in the United States and one in Canada, are cooperating in this seven-year trial. Four thousand men between the ages of 35 and 59 are being recruited. Subjects have an elevated blood cholesterol in the absence of severe hypertension, diabetes, endocrine disease, or other life-threatening disorders. They must be free of overt coronary heart disease or a history of heart ailments. Over 30,000 subjects have been screened and over 1,800 eligible volunteers have already been entered into the study. Recruitment should be completed by January 1976. The experimental group will receive a cholesterol-lowering diet plus the cholesterol-lowering drug, cholestyramine. The control group will receive the diet together with a placebo (inactive pill).

Hypertension Detection and Follow-Up Program (HDFP). Once it develops, primary hypertension, or high blood pressure, is a chronic, lifelong, usually incurable condition which almost always can be controlled with appropriate, continuing drug therapy. One of every seven adults in the United States is afflicted with hypertension. When uncontrolled, hypertension places undue stress on the heart and vascular system, leading to heart failure and kidney failure. Hypertension is also frequently linked with accelerated arteriosclerosis and its resulting complications, coronary occlusion and stroke. The disease is generally asymptomatic and its first clinical symptom is often one of these serious sequelae.

In recent years, effective drug therapy for the control of high blood pressure has been developed. However, half the Americans with high blood pressure do not know they have the disease. Of those who know, only half are being treated and, of those being treated, only half have their condition effectively controlled. This breakdown in effective hypertensive therapy exists because both patients and health professionals are unaware of the seriousness of uncontrolled hypertension or its effective treatment.

The NHLBI Hypertension Detection and Follow-Up Program is a multi-center cooperative effort to test whether systematic antihypertensive therapy will significantly reduce morbidity and mortality. Fourteen community-based populations are involved in the program. Participants include men and women between the ages of 30 and 69 with mild, moderate, or severe disease. The sample populations include a cross-section of major ethnic and racial groups and socio-economic strata.

Initiated early in 1973, the Hypertension Detection and Follow-Up Program has screened over 160,000 persons and identified 23,000 with diastolic blood

pressure of 95 mmHg or higher. Of these, approximately 11,000 were randomized into the program in two treatment groups--half to stepped care and half to referred care. In stepped care as carried out by the Program, the hypertensive is first treated with a diuretic. If this does not provide the desired decrease in blood pressure, additional anti-hypertensive agents are added to the treatment regimen in a time-sequenced, stepwise manner until the goal blood pressure is achieved. In referred care, the patient is treated by his private physician. Sixty-one percent of the patients continuing under either treatment have now attained and maintained their goal blood pressure.

Follow-up activities provide a direct measure of the prevalence, severity, and current treatment status of representative white and black populations with high blood pressure. The attainable reduction of complications of high blood pressure by organized screening and blood pressure management programs is being determined.

NHLBI-VA Clinical Trial in Mild Hypertension. This two-year collaborative study was initiated in 1974 as a pilot clinical trial. It is testing the feasibility of conducting a controlled clinical trial to determine whether treatment of mild hypertension results in reduction of the incidence of myocardial infarction. Subjects, age 21 to 50 years with diastolic blood pressure between 85 and 105 mmHg, have been identified in VA hospitals, industry, labor unions, university and community hospitals, and clinics. Four VA clinical centers have screened over 78,000 candidates during the past year. Nearly 600 men have been determined eligible and randomized into the study which will continue for another year. In addition to the pilot study results, this program will attempt to assess other problems related to undertaking a primary prevention clinical trial of mild hypertension. Such problems include patient availability within the proposed criteria, patient dropout rates during the one-year follow-up period, measurement of side effects and toxicity of anti-hypertensive medication, and the adequacy of data handling systems and protocols.

Extracorporeal Membrane Oxygenators (ECMO). In July 1974, a collaborative three-year program, involving nine institutions, was initiated to determine whether extracorporeal membrane oxygenators ("artificial lungs") are lifesaving in patients with acute respiratory failure. An estimated 150,000 adult patients suffer from acute respiratory failure annually and, of these, approximately 40 percent die. The ECMO trial will attempt to establish whether this mortality can be reduced by providing auxiliary oxygen that does not induce oxygen toxicity. During periods of respiratory crisis, extracorporeal support will be provided for several days. The trial will determine whether such a period of support will allow the damaged lungs to recover to the point that auxiliary oxygen is no longer needed.

Conventional heart-lung machines used in cardiac surgery allow complete pulmonary bypass for approximately six hours, after which period severe blood damage occurs at the direct blood-gas interface. Animal studies have shown that the extracorporeal membrane oxygenators can provide "long-term" (one to

two weeks) support to the lung without serious blood damage because the circulating blood and the oxygenating gases are separated by delicate gas-permeable plastic films. It is during gentle passage through a series of such films that the blood exchanges its carbon dioxide for oxygen.

This collaborative program is comparing the results in patients receiving conventional lung ventilating modes of therapy with the results in others who are receiving both conventional and ECMO therapies. The trial includes only patients in acute, but potentially reversible, failure where prospects of recovery are not otherwise dimmed by chronic diseases. The patients under study suffer from post-traumatic respiratory failure, pulmonary embolism, and adult respiratory distress syndrome.

Coronary Artery Surgery Trial (CAST). This seven-year study was initiated in 1972 on the recommendation of the National Heart, Lung, and Blood Advisory Council. It will evaluate the efficacy of coronary artery bypass surgery and its potential therapeutic value in reducing morbidity and mortality in coronary heart disease. Results of coronary artery surgery will be compared with nonsurgical medical treatment in patients where medical opinion differs as to the most appropriate type of therapy. At present, more than 40,000 such operations, costing more than $400 million, are carried out in the United States annually without definitive information on their long-term effect on patient survival. A substantial fraction of these operations are done in clinical circumstances in which the advantages of surgery over purely medical management remains to be determined.

The study involves 11 participating clinical centers and a coordinating center. All patients undergoing coronary angiography at the participating institutions have their data entered into a registry. Patients who fulfill the criteria for one of four sharply defined subsets, and who are judged to have equally favorable prognosis whether surgically or medically managed, are invited to participate in a formal randomized allocation between these two forms of therapy.

Planning and protocol phases have been completed, and an experimental data base has been established by entry of pilot data for over 1,500 patients into the patient registry. The entire CAST Program was recently reviewed by a non-Federal ad hoc scientific group which provided advice to NHLBI concerning implementation and conduct of the full-scale clinical trial. A two-year period of patient recruitment is now beginning. This will be followed by a five-year period of patient follow-up and an additional year of data analysis.

Unstable Angina Pectoris Trial. This randomized clinical trial was planned in 1972 to compare coronary artery bypass surgery with maximal medical therapy in patients with unstable angina pectoris (heart pain). The clinical symptoms of these patients simulate those of acute myocardial infarction, but the patients have no physical evidence of acute heart muscle damage. From 1972 through June 1975, over 180 patients were entered into the randomized trial. Approximately half received medical and half surgical treatment. Data

from 150 patients, now followed for one year, indicate mortality rates to be essentially the same for the two groups, both acutely during hospitalization and through an average follow-up period of six to nine months. During the initial hospitalization, heart attacks developed more commonly in patients receiving surgical treatment. However, symptoms of angina were totally or markedly relieved in approximately 85 percent of the surgically treated patients, but in only about 40 to 45 percent of medically managed patients. To achieve sufficient data for statistical evaluation, a total of 300 patients will be followed for a minimum of two years each.

Aspirin Myocardial Infarction Study (AMIS). The Aspirin Myocardial Infarction Study, initiated in 1974, is a three-year trial to determine whether administration of aspirin to persons who have had at least one documented myocardial infarction (heart attack) will result in a significant reduction in mortality. Planning and establishment of standard protocols are complete and patient recruitment was recently initiated. Aspirin produces inhibition of certain blood platelet functions and interferes with thrombotic events in some experimental systems. Preliminary clinical studies of coronary patients provided suggestive evidence that aspirin may prevent recurrent heart attacks.

Thirty clinical centers, a coordinating center, a central laboratory, and an electrocardiographic center are engaged in the AMIS Study. A total of 3,600 to 4,000 men and women between the ages of 30 and 70, meeting the criteria for participation, will be enrolled in this double blind, randomized clinical trial to determine whether or not the survival of coronary patients is increased by daily ingesting one gram of aspirin.

Hepatitis B Immune Globulin Clinical Trials. Two three-year clinical trials have just been completed, establishing that an effective, but temporary, protection against hepatitis B is now at hand. Hepatitis, which may lead to chronic liver disease, is the most frequent serious complication encountered in transfusing blood or blood products. An estimated 20 to 30 thousand transfused patients contract hepatitis each year. While less than one percent of these become fatalities, of those acutely infected, up to 5 percent become chronic carriers of the virus and may transmit the infection to others.

Two serum gamma globulin preparations, one with intermediate and one with high levels of antibodies against hepatitis B antigens, were tested during the clinical trials. A gamma globulin containing a normal level of antibodies was used as the control preparation.

The study was performed in hospitals and dialysis centers across the country. Participants in one trial included 712 medical workers and laboratory personnel who had been exposed accidentally to hepatitis B virus infections. The second trial involved 612 recently admitted patients and recently hired employees at renal dialysis units, where there is greater-than-normal risk of exposure to the hepatitis virus.

In both trials, the intermediate level antibody preparation resulted in essentially the same incidence of hepatitis as that of the control population. However, the incidence of hepatitis among participants given preparations with high levels of hepatitis B antibody was only about one-third that of the control group. Follow-up studies for nearly a year indicate that while the protection conferred by the antibody-rich gamma globulins is highly significant, it is only temporary and may, in fact, impede the development of "natural" immunity that sometimes results from exposure to hepatitis B antigen.

PREVENTION, CONTROL, AND EDUCATION PROGRAMS

"There are not two sciences. There is only one science and the application of science and these two activities are linked as the fruit is to the tree."
Louis Pasteur (1822-1895)

However illuminating, biomedical research results must first receive widespread dissemination and application if they are to improve the quality of life. Considerable knowledge has been acquired in recent years concerning many of the diseases under the NHLBI mandate, and an active program of prevention, control, and education is underway to speed this knowledge into the mainstream of clinical medicine. In response to the 1972 Act, the Institute has acted boldly in this new area of responsibility to develop the novel approaches needed to carry out this mission. Advice and guidance is being sought from behavioral and social scientists, nutritionists, and others.

Prevention, control, and education programs can be costly. But, as they may in the long run save billions of dollars, the Institute has moved ahead in this area as rapidly as possible. Major efforts are underway. However, no specific funds have been made available for prevention, control, and education programs. If these programs are to continue without specific curtailment in other Institute activity, the appropriation of funds as authorized by Section 414(b), Public Law 92-423, is urgently required.

The following section presents some of the Institute's newly initiated prevention and control activities in hypertension, arteriosclerosis, sickle cell disease, emergency treatment of cardiac and respiratory failure, recognition and treatment of neonatal respiratory distress syndrome (hyaline membrane disease), and rehabilitation of heart attack victims. A major working conference on health behavior held by NHLBI is also discussed. In addition, the National Research and Demonstration Centers each have major prevention, control, and education programs. These are discussed in the descriptions of these Centers presented earlier in this chapter.

National High Blood Pressure Education Program (NHBPEP). The mission of the National High Blood Pressure Education Program is to reduce death and illness associated with hypertension through an education program directed

at both the general public and health professionals. Goals of the program are:

- To reduce, by 1978, the number of persons in the United States having a diastolic blood pressure greater than 104 mmHg from the present level of 4.8 million to 2.4 million

- To increase opportunities for the public to obtain appropriate blood pressure measurement and increase the rate at which the public seeks treatment after referral

- To increase the number of health care practitioners following best medical practice for the detection, referral, and treatment of hypertension.

Uncontrolled high blood pressure is a major public health problem. It is the primary cause of 20,000 deaths and a contributing factor in 1,500,000 heart attacks and strokes that occur each year in the United States. An estimated 23 million Americans have high blood pressure.

The National High Blood Pressure Education Program is coordinated by the National Institutes of Health (NIH), with the National Heart, Lung, and Blood Institute as the focal point. The collaborative government/private sector effort also involves the Food and Drug Administration (FDA), the Health Resources Administration (HRA), the Veterans Administration (VA), and the Department of Defense (DOD), as well as over 150 private sector organizations, including professional societies and associations, voluntary health organizations, certifying and accrediting bodies, pharmaceutical companies, labor management groups, and insurance companies. All are working together to focus attention on high blood pressure as a serious disease, but one which can be readily detected and controlled. Activities of the program include:

- A High Blood Pressure Information Center which answers public inquiries about high blood pressure and prepares and distributes free educational materials.

- A Community Consultation Service which has recruited and provided orientation for 30 non-Federal consultants to offer technical assistance to community programs and local personnel. The service has maintained a caseload of 60 active community programs and provided assistance to 210 communities.

- National High Blood Pressure Month, May 1975, which was sponsored or endorsed by 129 organizations and over 300 community groups. Approximately 55,000 kits containing education and detection guidelines were requested.

The statistical data [7] below provide an indication of the effectiveness of the program:

- In calendar year 1974, the total number of patient visits for treatment of high blood pressure increased by 21.1 percent over 1973 and by 41.6 percent over 1971, the base year. In comparison, the total number of medical visits for all causes increased by only 16 percent in 1974 over 1971.

- In calendar year 1974, the number of new patient visits for treatment of high blood pressure increased by 38 percent over the 1971 visits whereas total number of new patient visits for all causes increased by only 18 percent during the same period.

Planned future activities of the National High Blood Pressure Education Program include:

- A high blood pressure exhibit incorporating blood pressure screening for inclusion in the DHEW bicentennial health exhibits program

- A demonstration and evaluation project to measure the utility of community high blood pressure coordinating councils

- Evaluation of patient tracking systems used in hypertension control programs

- Development of a system to quantify drug induced side effects of anti-hypertensive agents.

National High Blood Pressure Education Research Program (NHBPERP). The High Blood Pressure Education Research Program supports educational research to explore cost-effective ways to achieve a greater degree of blood pressure control in hypertensive patients.

This year-old program is supporting behavioral research in health education, attitudes, motivation, and compliance as they relate to the prevention and treatment of hypertension. A research effort to identify effective education methods which will increase hypertensive patient adherence to therapy is also being undertaken. Studies are being planned to delineate the characteristics of hypertensive individuals who would benefit from specific educational approaches aimed at adherence behavior.

National Sickle Cell Disease Program. The Sickle Cell Disease Program is a major effort within the National Program. Sickle cell trait, one of the most common inherited blood abnormalities in the United States, is believed to be carried by more than two million Americans, primarily black. However, most of these carriers are healthy. If two carriers marry, each of their children has a one in four chance of having sickle cell anemia, a disease which affects approximately 50,000 individuals. It is a hereditary blood disorder characterized by the presence of chronic anemia, jaundice, recurrent episodes of pain called "crises," growth retardation, an increased susceptibility to certain infections, a decreased physical capability, and, frequently, a shortened lifespan. About one in 500 black babies in this country is born with sickle cell anemia. First described in 1910, this serious disease received only limited attention for more than 60 years.

The National Sickle Cell Disease Program was initiated in 1971 as a major collaborative effort to accelerate research in, and to improve diagnosis, control, and treatment of, sickle cell anemia.* The National Institutes of Health (NIH) was named as the lead agency for the overall program and it is also responsible for its research and development activities. A National Sickle Cell Disease Advisory Committee, appointed by the Secretary of DHEW, developed recommendations on program direction and policy which resulted in the establishment of Comprehensive Sickle Cell Centers, Sickle Cell Screening and Education Clinics, a mission-oriented research and development program, biomedical research, a public and professional education program, and a hemoglobinopathy training program.

The NHLBI, within the NIH, serves as the lead institute and coordinates the activities of the overall program. The Health Services Administration (HSA) is responsible for some of the demonstration activities in education, testing, and counseling. Other agencies actively engaged in related sickle cell activities include the Center for Disease Control (CDC), the Department of Defense (DOD), and the Veterans Administration (VA).

In 1975, 15 comprehensive Sickle Cell Centers and 26 Screening and Education Clinics were active. Summarized below are a few recent accomplishments:

- The programs of a number of Screening and Education Clinics have been evaluated to identify the best techniques for testing, counseling, and patient referral. The Clinics have screened approximately 420,000 individuals during FY 1975. Of these, an estimated 40,000 will receive special counseling.

- A National Symposium on Sickle Cell Disease was held in late FY 1974 and its proceedings have been published [8].

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* The National Sickle Cell Anemia Control Act in May 1972 provided for nearly identical objectives and programs to those which had already been implemented in the 1971 Plan.

- Basic research has been supported on cell structure, the synthesis of hemoglobin, improved detection and identification of abnormal hemoglobins, and flow patterns exhibited by cells containing sickle hemoglobin.

- Factual information has been provided to the public through a variety of vehicles.

- A training program in the detection of abnormal hemoglobins and a series of hemoglobinopathy workshops have been conducted by the Center for Disease Control (CDC). A hemoglobinopathy laboratory manual [9] has been published by CDC, and Reference Laboratories giving advice on the identification of abnormal hemoglobins have been established.

Recognition and Treatment of Acute Respiratory Distress in Adults. Two educational programs are being developed for early treatment of acute respiratory insufficiency to reduce the morbidity and mortality resulting from this disease. The first program is aimed at physicians with no special training in respiratory disease; the second is for non-physicians likely to have first contact with patients suffering from acute respiratory insufficiency. Both innovative and well-established educational methodologies are being employed. Three approaches to information dissemination are being tested concurrently in order to assess their relative effectiveness.

Recognition and Treatment of Acute Respiratory Distress in Infants. At present, the most common cause of death in the newborn is respiratory failure. It may be prevented if respiratory insufficiency can be anticipated or recognized at onset and therapeutic measures instituted promptly. To identify those infants at risk requires recognition of prenatal conditions in the mother and perinatal conditions in the infant which may lead to respiratory problems in the neonate. Prematurity, which is frequently associated with neonatal respiratory distress syndrome (hyaline membrane disease), must also be recognized and treated without delay if a maximum number of infants are to be saved.

The educational programs being developed are directed to physicians, nurses, physician's assistants, midwives, and other professionals involved in prenatal care, delivery, and neonatal care. These individuals are being taught to recognize respiratory distress and initiate early treatment. The educational programs are for use in those geographic areas and community settings lacking intensive care facilities for neonates.

A Unified Hemophilia Program. The hemophilias are inherited bleeding diseases occurring almost exclusively in males. The affected gene is transmitted via the female sex chromosome to one in two of her male offspring. Although

the known hemophilia population of this country is only approximately 25,000, hemophilia constitutes a major national health problem. Its treatment presents one of the largest single demands upon the nation's blood resources; it is extremely expensive; and it must continue for the lifetime of the patient. The estimated current yearly cost to replace the missing clotting factor is in excess of $6,000 per patient, or more than $120 million for the 80 percent of hemophilia patients who benefit from such replacement.

In cooperation with the National Hemophilia Foundation, the Institute is attempting to develop a pilot education program on the care of hemophilia both for professionals and for the public. However, before a feasible education program could be designed that would be effective and that would not raise expectations and demands which were impossible to meet, careful consideration had to be given to some major problems that might arise. The availability of blood, the type of hemophilia care system currently in existence, payment mechanisms for such care, and availability of trained manpower had to be assessed.

To approach this complex task, NHLBI used the technique of "gaming," or situation modeling, whereby plausible, but hypothetical situations were created in "pretend" time. This allowed the decision-makers to develop strategy and approaches that could be used in real time. The participants in the situation modeling sessions included educators, blood bankers, physicians, insurance experts, and one hemophilia patient. They considered the effect of total insurance coverage on blood resources, available care systems, available financing, etc. Data from the situation modeling sessions, while still under analysis, have already been helpful in formulating program goals.

Working Conference on Health Behavior. Considerable knowledge is already available on the prevention and control of the two major cardiovascular disorders--hypertension and arteriosclerosis. Similar information exists to aid in the prevention of chronic respiratory diseases. Effective dissemination of the known facts concerning sickle cell disease and hemophilia could lessen the suffering caused by these diseases. Early recognition by the patient of the signs of an acute heart attack, the acceptance of his (or her) disease, and the seeking of immediate treatment could save many lives. Application of the latest and best techniques of cardiac rehabilitation could decrease further the morbidity and mortality from heart attacks.

To facilitate such prevention, control, and education activities, the NHLBI initiated an assessment of the state of the art in continuing medical and public education and an evaluation of current developments in these fields by organizing a Working Conference on Health Behavior.* This multidisciplinary group of 50 expert consultants and 22 Institute staff members met for a four-day period of intensive discussion and writing. Prior to the meeting, conference participants were assigned to one of the following major task groups: Hypertension, Arteriosclerosis, Cardiac Rehabilitation, Prevention of Chronic Pulmonary Disease, and Blood Donor Recruitment. Each task group prepared a position paper. Conference participants, in smaller groups,

* The conference was held at Basye, Virginia, in May 1975.

prepared working papers on the following broader issues: Life Style Development Versus Modification; Individual Responsibility for Health Maintenance; Psychosocial Determinants for Illness Versus Health; Social Sequelae of Illness; Ethical Concerns Regarding Health Behavior; Compliance; Recruitment and Coping. A complete report of this conference has been published [10].

During the conference, behavioral and social scientists, psychiatrists, "treating" physicians, epidemiologists, biological researchers, nutritionists, nurses, and education specialists learned each other's language and defined a common terminology to be used and understood by all. Through this interdisciplinary crossfertilization many new approaches were developed and working relationships were built across disciplinary barriers which will greatly facilitate future progress towards the following broad objectives:

- Establishment of factors that will motivate public awareness of health problems and stimulate health checkups
- Characterization and evaluation of differences in knowledge, attitudes, and behavior of persons who participate poorly, or not at all, compared to those who participate fully in therapy
- Definition of improved, cost-effective methods to deliver professional, consumer, and patient education and to identify methods of increasing patient adherence to positive health behavior patterns
- Encouragement of experts in psychology, sociology, and behavioral and nutrition research to investigate problems associated with health education, motivation, and compliance as they relate to health problems and to the therapy and rehabilitation of patients with chronic disease
- Investigation and improvement of the knowledge, attitudes, and behavior of health care professionals in relation to patient treatment and rehabilitation.

OTHER SPECIAL INITIATIVES

Development of Animal Models of Human Disease. Animal models permit studies not possible in humans. They are an essential prerequisite to human studies. The more accurately the animal model of a pathogenic condition mirrors the human disease, the less human experimentation will ultimately be needed.

Such models can be used to monitor and assess physiological, biochemical, metabolic, genetic, immunological, functional, and behavioral parameters of disease as well as to observe the effects of disease therapy. Examples of current and planned use of animal models in the National Program are summarized below:

- A report of the conference "Research Animals in Medicine" [11], containing useful animal model guidelines, has been published.

- The genetically spontaneously hypertensive rat is a good model of human essential hypertension. Guidelines for its use have been developed in collaboration with the Institute for Laboratory Animal Research.

- NHLBI has assisted in the establishment of a resource colony of stroke-prone hypertensive rats through the NIH Small Animal Section, Division of Research Services.

- A resource colony of 20 strains of hypertensive rats with systolic blood pressures between 100 mmHg and 200 mmHg is being used to assess various physiological, biochemical, and behavioral parameters in the etiology of hypertension.

- Dogs having genetic electrical conduction disturbances of the heart are being used for electrophysiological and histophysiological studies. Elucidation of conduction pathways in the hearts of these dogs may provide insight into mechanisms of human heart rhythm disturbances.

- Animal models have been developed which allow continuous monitoring of cardiovascular parameters in the living intra-uterine animal fetus. Baseline physiological, metabolic, and morphological data are being gathered in the normal animal fetus as well as in the animal fetus with surgically produced cardiac defects.

- Baboons can be conditioned to smoke and probably to inhale. The use of such conditioned non-human primates to assess the relationship between smoking and disease is being tested.

- Non-human primate models of arteriosclerosis, hypertension, and dyslipoproteinemia are being developed. These models will facilitate research into the chronic development and regression of arterial lesions.

- A number of non-human primates will be screened for spontaneous or genetic lipid and hypertensive disorders. Monkeys with a rare Type II lipid disorder are under study.

- Animal models are being developed for physiologic, biochemical, hemodynamic, and metabolic studies of acute myocardial infarction.

- NHLBI is developing an animal model of pulmonary fibrosis to study the biochemical and immunological events involved in the pathogenesis of the fibrotic lung and to develop new approaches to therapy and prevention.

- Dog models have been developed for study of pathophysiologic effects of pulmonary hypertension on right heart function. Pulmonary artery banding and balloon catheter inflation have been used to produce chronic and acute models.

- A new model of human neonatal hyaline membrane disease is the fetal Macaque monkey, delivered 30 to 40 days prematurely by Caesarian section. Pathologic examination of lung tissue confirms these monkeys have hyaline membrane disease.

- An animal (rabbit) model of hypersensitivity penumonitis has been developed which parallels most of the clinical and immunologic findings of the human counterpart.

- Hepatitis B is transmitted by blood and blood products. The NHLBI is establishing a chimpanzee model which is serologically negative for hepatitis B antigen (HB_SA_9) and an antibody to this antigen (anti-HB_S) for use in hepatitis research. A colony of chimpanzees will be available for selective investigations of hepatitis.

Noninvasive Instrumentation. Invasive methods of disease detection are frequently complex, require expertise, and none is totally risk-free. Improved methods to detect, characterize, and quantify atherosclerosis are essential. They are needed to detect clinical disease and to evaluate prognosis. Research and clinical trials pertaining to prevention or regression of arteriosclerotic lesions would be greatly shortened and would be far less expensive if noninvasive measures were available because earlier endpoints than death or catastrophic disease could be employed.

A very important recent development has been the establishment of NHLBI programs for development of noninvasive methods and instrumentation. At the present time, phonoangiography has been developed as a functional noninvasive technique for detection of arteriosclerosis. In a related development, computer methods have achieved image enhancement and quantification of arterial disease of conventional femoral arteriograms.

NHLBI studies also show that echocardiography, a painless, safe, noninvasive technique for visualizing the heart and great vessels by means of reflected ultrasound, is proving to be extremely useful in the diagnosis and evaluation of a variety of congenital and acquired heart conditions. A scanner placed on the patient's chest directs an ultrasonic beam through the intact chest wall at the section of the heart to be examined. Like X-rays, ultrasound passes readily through body tissues and fluids, but a portion of the beam is reflected from the surface of the heart and from the blood-tissue interfaces within it. The returning echoes are converted into a cross-sectional image of the heart, permitting detection of structural defects and assessment of their effects on heart performance.

NHLBI is undertaking a program to develop noninvasive sensors to continuously monitor blood gas tension for use in neonates and/or adults in respiratory distress. Promising sensor designs will be evaluated for clinical feasibility and to confirm their clinical utility. The most promising sensors will undergo clinical testing.

A major program during the past several years has been directed at protecting ischemic myocardium and minimizing infarct size. A closely related program involves development of quantitative, reproducible, and safe methods which can be used on acutely ill patients to measure the size of ischemic, infarcted, and scarred myocardium. Currently, three approaches for quantifying infarct size are under investigation. One of these is a noninvasive technique involving precordial measurement of the electrocardiogram. Integration of ST segment abnormalities (i.e., ST segment mapping) provides a measure of the extent of ischemia. Corroborative histologic evidence shows that ST segment mapping techniques are highly valid. A second noninvasive technique is the determination and interpretation of the blood levels of enzymes related by damaged heart muscle. A third method uses radioisotope techniques. Some radioisotopes go to heart muscle which is normally perfused and, chemically, behaves normally; that is, the uninvolved muscle. Other radioisotopes go to muscle which has had membrane damage and is ischemic. Thus, both the normal and the abnormal heart muscle can be identified.

Protection of Ischemic Heart Muscle. Most heart attacks stem from drastically reduced or completely blocked blood flow to the portion of the heart muscle normally serviced by an artery that is suddenly obstructed. The result is an area of blood-deprived, damaged, or dead muscle. The extent of irreversible heart-muscle damage following the acute attack is often a crucial factor affecting both survival and the amount of residual disability after recovery. Experimental studies utilizing noninvasive techniques to measure infarct size indicate that the usual destructive effects of acute heart attacks on the heart muscle can be minimized by timely and appropriate clinical interventions.

Reducing the workload of the heart by careful administration of drugs to slightly reduce the blood pressure, or by mechanical devices (e.g., the "intra-aortic balloon") have shown encouraging results in limited clinical studies. Several promising drugs increase blood flow to the heart muscle, some by reducing swelling, others by dilating vessels. Others apparently alleviate

coronary artery blockage by increasing diffusion of nutrients into the tissue. The provision of glucose in high concentrations in the presence of potassium and insulin provides a higher concentration of nutrients to the starved muscle and appears to be beneficial. These results suggest that a more aggressive approach based on sound physiological and clinical principles might save many lives and restore, to a normal existence, many persons who would otherwise be permanently disabled following a heart attack.

IV. Coordination Efforts

Major formal cooperative and collaborative efforts, both national and international, are being undertaken by NHLBI. Numerous informal, but highly effective, interactions also exist. While collaborative efforts with other organizations do not represent a new Institute initiative in response to the 1972 legislation, the Act does require the establishment of an Interagency Technical Committee on Heart, Blood Vessel, Lung, and Blood Diseases and Blood Resources.

The National Program with its broad, long-range goals provides an opportunity to stimulate collective efforts within and outside government with groups which represent all sectors of society. The multiplier effect of this cooperative effort maximizes the Institute's resources and extends the National Program well beyond its immediate sphere of influence. The NHLBI collaborative efforts fall into five major areas. They consist of cooperation with:

- Other bureaus, institutes, and divisions of the National Institutes of Health
- Federal agencies exclusive of the National Institutes of Health
- Professional societies
- Voluntary organizations
- Scientists in other nations.

The coordination efforts described in this chapter include important examples of formal interagency coordination, other interagency and intra-agency coordination, as well as international collaboration. Expansion and refinement of these collaborative approaches is an ongoing NHLBI activity.

INTERAGENCY TECHNICAL COMMITTEE

The key formal mechanism for coordinating efforts related to the National Program is the Interagency Technical Committee on Heart, Blood Vessel, Lung, and Blood Diseases and Blood Resources (IATC). The IATC was established by the Secretary of the Department of Health, Education, and Welfare in November 1972, in accordance with the National Heart, Blood Vessel, Lung, and Blood Act

of 1972. This Committee, chaired by the Director of the National Heart, Lung, and Blood Institute, coordinates Federal agency activities related to heart, blood vessel, lung, and blood diseases so as to assure their adequacy and technical soundness. The Committee provides a forum for communication and exchange of necessary information. It consists of representatives from each of the constituent agencies and departments shown in Table 3.

The NHLBI, in cooperation with the IATC members, compiled and published an inventory of ongoing programs related to the National Program in FY 1972 and FY 1973. This information has now been updated to include FY 1974. The update has identified extensive research and study activities by IATC member agencies which relate to the 23 major categorical disease problem areas included in the National Program. Table 4 summarizes these related activity areas which include a total of more than 3,550 research projects, exclusive of those at NHLBI.

Summary descriptions of the most important related programs were published covering FY 1972 [12], FY 1973 [13], and FY 1974 [14]. These publications serve to improve communication and exchange of information on the National Program not only among IATC member organizations, but also among the scientific community in general. The volumes are widely disseminated within NHLBI, the NIH, and other member departments and agencies of the IATC as well as non-Federal organizations with missions related to the National Program. This programmatic information assists Federal and non-Federal organizations to formulate plans and to implement and coordinate projects addressing the goals of the National Program.

The information is also supplied to scientists and administrators at health professional schools, universities, colleges, and other institutions. It provides an extensive review of Federally supported research in areas related to heart, lung, and blood diseases. These publications aid scientists and administrators in identifying the Federal funds available for various

TABLE 3.
MEMBERS OF THE INTERAGENCY TECHNICAL COMMITTEE

AGENCIES OF THE DEPARTMENT OF HEALTH, EDUCATION, & WELFARE	OTHER DEPARTMENTS AND AGENCIES OF THE FEDERAL GOVERNMENT
Alcohol, Drug Abuse, and Mental Health Administration	Department of Agriculture
Center for Disease Control	Department of Defense
Food and Drug Administration	Department of Transportation
Health Resources Administration	Energy Research and Development Administration
Health Services Administration	Environmental Protection Agency
National Institutes of Health	National Aeronautics and Space Administration
Social and Rehabilitation Service	National Science Foundation
Social Security Administration	Veterans Administration

TABLE 4.
NATIONAL PROGRAM RELATED ACTIVITY AREAS

	PROBLEM AREA	NIH COMPONENTS												OTHER FEDERAL AGENCIES														
		NCI	NEI	NIAID	NIAMDD	NICHD	NIDR	NIEHS	NIGMS	NINCDS	NLM	DRR	FIC	USDA	ADAMHA	EROA	CDC	DDD	EPA	FDA	HRA	HSA	NASA	NSF	SRS	SSA	DOT	VA
HEART AND BLOOD VESSEL DISEASES	Arteriosclerosis				●	●	●	●	●		●	●		●	●	●	●					●		●				●
	Hypertension	●	●	●	●	●	●		●	●	●	●		●	●	●	●				●	●	●					●
	Cerebrovascular Disease				●	●			●	●		●			●	●					●	●	●	●				●
	Coronary Heart Disease				●	●		●	●		●	●			●	●	●	●	●		●	●	●	●	●			●
	Congenital and Rheumatic Heart Diseases			●		●	●		●		●	●				●			●			●		●				●
	Peripheral Vascular Diseases	●	●		●		●		●					●	●	●	●			●			●	●				●
	Cardiomyopathies and Infections of the Heart			●	●	●	●					●		●	●	●			●									●
	Arrhythmias					●			●			●			●	●	●	●	●			●	●	●	●				●
	Heart Failure and Shock			●		●			●			●			●	●		●			●		●	●				●
	Circulatory Assistance								●			●			●	●												
	Heart and Blood Vessel Diseases (Multicategorical/Other)	●	●	●	●	●	●	●	●	●	●	●	●	●	●		●		●		●	●	●	●			●	●
LUNG DISEASES	Structure and Function of the Lung				●	●	●	●	●			●		●	●	●	●		●				●	●				●
	Pediatric Pulmonary Diseases			●	●	●			●			●										●						
	Emphysema and Chronic Bronchitis	●		●		●		●	●			●		●		●	●		●		●				●			●
	Fibrotic and Immunologic Lung Diseases	●		●	●			●	●			●		●	●	●	●		●			●		●				●
	Pulmonary Vascular Diseases					●			●			●				●												●
	Respiratory Failure			●		●			●			●				●									●			●
	Lung Diseases (Multicategorical/Other)	●			●	●		●	●			●		●		●	●		●		●	●			●			
BLOOD DISEASES AND BLOOD RESOURCES	Bleeding and Clotting Disorders	●		●	●	●	●		●			●		●	●	●								●				●
	Sickle Cell Disease and Other Disorders of the Red Blood Cell	●	●	●	●	●	●		●			●		●	●	●			●			●		●				●
	Biomaterials				●		●		●										●					●				
	Nationwide Blood System	●			●				●			●						●			●							
	Safety of Blood Therapy	●		●	●	●			●			●			●	●	●	●		●		●	●					●
	Blood Component Therapy	●							●			●		●		●		●										
	Transplantation Biology	●	●	●	●	●	●		●			●			●	●		●										●
	Blood Diseases and Blood Resources (Multicategorical/Other)			●	●	●	●	●	●			●			●			●			●	●	●	●				

categories of research addressed by the National Plan as well as which Federal departments and agencies administer these funds.

Plans have been developed for a further in-depth review of the complementary activities of the member departments and agencies of the IATC. An intensive analytic effort is in its early stages. It will identify, for each category within the NHLBI Program, the areas of gap, overlap, and duplication of efforts. Progress within each problem area will be evaluated against goals and objectives stated in the National Plan. The aim of this review is to aid in the formulation of future policy as to the direction and scope of the IATC members' collaborative efforts. Better collaborative efforts at the operational level are also envisioned as a result of this review.

OTHER INTERAGENCY AND INTRAAGENCY COORDINATION

A number of major cooperative and collaborative efforts have been implemented by each of the Divisions of the National Heart, Lung, and Blood Institute. Some involve inter-Division or interprogram coordination; others involve other Federal agencies, non-Federal organizations, professional societies, or elements of the private sector. Examples of efforts, wholly or partially supported by the National Heart, Lung, and Blood Institute, are summarized below.

Blood Resources Program. Blood is a valuable, but limited, natural resource. The demand for blood is increasing as new therapies are developed, while the supply of high quality blood remains limited. The ever-expanding need for blood demands its safe and efficient utilization. In 1972, the National Heart, Blood Vessel, Lung, and Blood Act significantly expanded the authority and responsibility of the NHLBI in areas which include the use of blood, blood products, and the management of our nation's blood resources.

The Blood Resources Program has, under the guidance of NHLBI, developed and supported programs aimed at assuring the availability of an adequate supply of high quality blood and blood products. The activities supported by the program include research and development in the following areas:

- Management of the National Blood System to optimize utilization of blood resources through development of technology, methods, and procedures as well as collaborative efforts involving the Bureau of Biologics (FDA) and the Health Resources Administration (HRA) within the government and the American Blood Commission (ABC) in the private sector

- Improvement in the safety of blood and blood product use through applied research on hepatitis virus, cytomegalovirus, plastic toxicology, and fail-safe matching procedures

- Efficient utilization of blood component therapy through development of better separation and preservative methods, better definition of specific use indicators, better methods to assess effectiveness, and education of physicians regarding optimal use of blood components

- Improvement of public and professional understanding of blood donation.

The NHLBI and the National Program participated in the formation of the American Blood Commission (ABC) during 1974 and 1975, and the NHLBI has contracted with the ABC for several task forces whose efforts will have a major impact in providing the data upon which the Commission will implement the goals of the National Blood Policy. A number of studies are in progress or have recently been completed under the National Blood Resources Program. Most are directly related to the work of the American Blood Commission and the goals of the National Blood Policy:

- A study on "Regionalization in Blood Supply Systems" has been completed.

- A project to develop a blood establishment inspection and registration system (BEIRS) is being developed by the Bureau of Biologics. The NHLBI is supporting part of this effort. This national blood resource information system will collect, process, store, and report information on the use of blood and blood products.

- The NHLBI and the Health Resources Administration (HRA) are jointly supporting three American Blood Commission Task Forces studying the organization and management of Blood Banking and of a National Blood Resource Data System.

- Prototype sterile connecting devices for use between plastic containers have been developed during the past year. Preliminary bacteriologic studies indicate that they allow interconnection without contamination so that they have many applications in blood banking practice. For example, they permit extension of the outdating period for thawed, washed red cells, and they may simplify other blood banking operations. Their low cost, estimated at 3 cents per bag, makes their wide use economically feasible.

Other interagency activities include:

- Establishment of a Hepatitis Policy Committee and a Hepatitis Liaison Committee with the National Institutes of Health (NIH), the Food and Drug Administration (FDA), the Department of Defense (DOD), and the Veterans Administration (VA)

- Establishment of an Interagency Coordinating Committee with the Office of the Assistant Secretary for Health (ASH) for the implementation of National Blood Policy and operation of the American Blood Commission (ABC).

Smoking. Cooperative efforts to reduce smoking and to study and detail its harmful effects on health are being conducted by several Federal agencies, including the National Heart, Lung, and Blood Institute, the Center for Disease Control's National Clearinghouse for Smoking and Health, and the Veterans Administration.

The Tobacco Working Group within the National Cancer Institute is cooperating with the NHLBI on a program to bioassay cigarettes that are modified to be less carcinogenic and less pathogenic for chronic lung disease, arteriosclerosis, and heart disease. Modified cigarettes have been developed in the NCI program, carcinogenic activity towards mouse skin is under study, and inhalation models for lung cancer are being developed.

Preliminary model development for bioassay in chronic pulmonary and cardiovascular disease has begun. A pilot NHLBI study has demonstrated that baboons can be conditioned to smoke and probably to inhale. This study will refine the instrumentation to measure and analyze the smoking inhalation characteristics of the baboon for comparison with those of man. The smoking baboons will be used to assess the effect of smoking on arteriosclerosis.

The National Clearinghouse for Smoking and Health is cooperating with NHLBI in a comprehensive smoking withdrawal program to develop a community-based control program. The medical profession has assumed that the successful acquisition, or elimination, of specific health related behavioral patterns is a long-term problem requiring extensive support and assistance in order to prevent "back sliding." However, recent studies have shown that 70 to 80 percent of the relapse, or "back sliding" to old habits, occurs within the first three months following initiation of behavioral change. New studies to confirm these results are planned. These results will be of significance for alcohol and drug control programs as well as for the smoking withdrawal program.

The epidemiological study of tobacco and health has revealed that in a population of 250,000 veterans, discontinuation for smokers who smoke two packs a day results in gradual reduction of cardiovascular mortality rates to

levels approaching those of non-smokers after about 18 years. For moderate smokers this return to control levels takes at least 10 years.

Hypertension. The High Blood Pressure Education Program, initiated in 1973, was designed to improve the control of high blood pressure among the nation's population through special efforts to educate professionals and the public. The program was originally coordinated by an interagency committee at the National Institutes of Health level. A new ad hoc group, the High Blood Pressure Coordinating Committee, has been formed which includes NHLBI, American Medical Association, National Medical Association, American College of Cardiology, Citizens for the Treatment of High Blood Pressure, Inc., American Hospital Association, American Heart Association, National Kidney Foundation, and representation from community programs and Departments of Public Health. The National Heart, Lung, and Blood Institute serves as the focal point for program implementation and coordination. Major collaborative efforts relating to the program are conducted by government agencies, professional societies and associations, voluntary health organizations, certifying and accrediting bodies, pharmaceutical companies, labor and management groups, and insurance companies, all working together to focus attention on high blood pressure as a serious, but readily detected and controlled, disease. Widespread dissemination of high blood pressure information and educational materials is being handled through all available channels of communication at the National Institutes of Health, the Department of Health, Education, and Welfare, the United States Congress, and local offices of the Professional Standards Review Organizations. Other related current Federal agency activities include:

- A survey among physicians by the Food and Drug Administration to determine baseline attitudes and practices relative to hypertension therapy
- A cooperative effort by the National Library of Medicine and the National Medical Audiovisual Center to develop professional education materials on hypertension therapy and patient education
- The development by the Walter Reed Hospital, Department of Defense, of a patient film on high blood pressure
- The direct involvement of the extension service of the Department of Agriculture in high blood pressure education and control activities.

A second National High Blood Pressure Month was held in May, 1975. Over 120 national organizations endorsed and participated in special activities during this month.

Nutrition. Direct collaboration among nutritionists from the National Heart, Lung, and Blood Institute, the U.S. Department of Agriculture (USDA), and the Food and Drug Administration (FDA) to update and publish a new authoritative nutrient composition source book is underway. It will provide the basic dietary data necessary for research on the effects of diet on blood lipids and heart disease. An updated provisional food table for certain important fat-containing food groups has been completed. The revised figures on the fatty acid composition of dairy products and beef represent the first update of fatty acid composition published by the USDA since 1955. The NHLBI sponsored an Ad Hoc Committee on Food Fats in Industry which reviewed the feasibility of obtaining better information on composition of food fats to enable revision and update, as necessary, of the food composition tables. The food fats and oils industry, university nutrition departments, USDA, FDA, and NHLBI were represented. Consistently accurate food composition data are difficult to obtain because of changes in fat and oil sources. Industry representatives agreed to provide the best available current information.

The close coordination of the large clinical trials within the Division of Heart and Vascular Diseases has resulted in the establishment of a single Central Nutritional Coding Center used by both the LRC and MRFIT Programs. Nutrition staff training and nutritional Code Book maintenance are now performed jointly by these two programs. Shortly, a computerized coding system will be made available to all groups potentially interested in the collection of standardized nutrition data.

A Nutrition-Behavior Conference brought together investigators from the Lipid Research Clinics, Multiple Risk Factor Intervention Trial, Specialized Centers of Research Program, and the National Cardiovascular Research and Demonstration Center to share the interim results of their studies. Some 100 members representing three related specialities--medicine, behavioral science, and nutrition--were brought together to explore how best to use the expertise of the behavioral scientists to augment the skills of the practicing nutritionists and physicians in efforts to change health-related dietary patterns within the U.S. population. Conference proceedings are available, and conference recommendations are being used to further nutrition-behavioral research within the National Program [15].

Diabetes. Diabetes mellitus is a hereditary disease characterized by a variable degree of carbohydrate (sugars and starches) intolerance and specific vascular lesions. Premature atherosclerosis is a major sequela of diabetes, which also leads to changes in both large and small blood vessels of the heart, brain, legs, and retina of the eye, and diabetes can also result in hypertension. As two of the most serious sequelae of this illness, arteriosclerosis and hypertension are major problem areas in the National Program and the NHLBI has a strong commitment to diabetes research and control.

In July of 1974, the National Diabetes Mellitus Research and Education Act was signed into law [16]. The Act called for the establishment of a National Commission on Diabetes to draw up a plan for a coordinated research program in diabetes. Because diabetes-related problems fall within the purview of their Institutes, the Directors of seven NIH Institutes--the National Institute of Arthritis, Metabolism and Digestive Diseases (NIAMDD), the National Eye Institute (NEI), the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), the National Heart, Lung, and Blood Institute (NHLBI), the National Institute of General Medical Sciences (NIGMS), the National Institute of Child Health and Human Development (NICHD), and the National Institute of Dental Research (NIDR)--were appointed to the Commission. Ten representatives of the non-Federal sector also serve on this Commission which is formulating a long-range plan for a National Program of research, education, and treatment of diabetes mellitus. The Act also authorized the Diabetes Coordinating Committee, chaired by the Director of NIH and consisting of the same seven NIH Institute Directors as well as representatives from all Federal departments and agencies whose programs involve health functions or responsibilities related to diabetes. This Committee provides background information to the Commission and is preparing a report for submission to Congress. NIAMDD is the lead Institute of this Committee. However, NHLBI, because of its strong commitment to diabetes-related research, intends to play a major role in its activities.

Pressure and Underwater Biomedical Research. The NHLBI is participating in a National Cooperative Program of Pressure and Underwater Biomedical Research and Operation Development with the Department of the Navy and the National Oceanic and Atmospheric Administration. The program is investigating the biomedical problems which result from increasing hydrostatic pressure. It is focusing on how the respiratory and cardiovascular and renal systems respond to increasing physical and physiological stresses over extended time periods. Initially, the stress on the respiratory system is compensated for by alterations in the circulatory and renal systems. As the limit of the compensatory processes is reached, continued stress leads to failure in functions which can progress to a complete breakdown of all homeostatic mechanisms within the body. The respiratory system is the prime target of this research, which promises to provide important insights into the structure and function of the lung.

National Sickle Cell Disease Program. The National Sickle Cell Disease Program is a cooperative program between NHLBI, the Health Services Administration, and the Center for Disease Control. Details of this program are presented in Chapter III.

INTERNATIONAL COLLABORATION

Heart, blood vessel, lung, and blood diseases transcend national boundaries. Therefore, cooperation with other nations in research on these diseases is important in strengthening the National Program. A major example of international collaboration closely related to fulfilling Institute goals is the US-USSR Health Exchange Program. Sporadic US-USSR scientific exchange in the cardiovascular area began in 1955. A formal cooperative effort was initiated in 1972. It is a highly structured program involving direct collaboration between American and Soviet scientists in mutually planned and executed research activities. The five-year term of the agreement which covers this program is now half completed and active cooperation is underway in six problem areas. Five of these areas are in the realm of cardiovascular diseases, the sixth is in the area of blood transfusion--with particular emphasis on the prevention of hepatitis and the use of blood in cardiovascular surgery. A second US-USSR collaborative agreement in the area of artificial heart research was signed in 1974. The NHLBI is the overall coordinator of U.S. scientific activities for both these cooperative agreements. Salient activities related to the National Program which are being conducted under these joint US-USSR agreements are summarized below.

Pathogenesis of Arteriosclerosis. Arteriosclerosis is the most common type of cardiovascular disease and the chief cause of death in both the U.S. and the U.S.S.R. A joint clinical study has been undertaken to determine the prevalence in both countries of hyperlipidemias and ischemic heart disease, and the role of diet on the risk of developing these diseases. The study involves large numbers of well-characterized subjects in each country. This comprehensive clinical study, using identical techniques based on carefully formulated research protocols and analyzed by highly standardized techniques, will provide data on the nature and relative magnitude of arteriosclerotic disease and its associated risk factors in the U.S. and U.S.S.R.

Management of Ischemic Heart Disease. Ischemic heart disease is the most common clinical complication of arteriosclerosis and the most common complication leading to death. Through the US-USSR agreement, a collaborative study is proceeding to systematically assess and compare the way in which well defined heart disease patients are treated in the two countries. The ultimate goal of the studies, which involve coordinating a domestic U.S. program with a domestic U.S.S.R. program, is to assess various medical and surgical therapies for the treatment of ischemic heart disease. These therapies include: "differential" intensive medical management in the U.S.S.R., "conventional" medical management in both countries, and coronary artery bypass surgery in the United States. Scientists from both countries have met on four occasions to standardize terms, methods, and forms for the study, and to characterize the patient groups which will be compared.

Myocardial Metabolism. The biochemistry and performance of both the healthy and the diseased heart muscle are being studied in an attempt to find solutions to problems associated with ischemic and other types of heart disease.

Myocardial metabolism studies are complex and require a high degree of specialization. Joint US-USSR symposia on myocardial metabolism were held in 1973 in the U.S.A. and in 1975 in the U.S.S.R. to exchange information and promote scientist-to-scientist contacts. A number of leads and ideas were identified as the basis for possible future collaborative efforts. Tentative areas proposed include: studies of ischemic heart muscle, techniques for limiting the extent of heart muscle damage following a heart attack, and the effect of hormones and other factors on the metabolism, blood circulation, and function of the heart muscle. The Proceedings of the 1973 Symposium [17] have been published in English and in Russian and disseminated to the scientific communities in both countries. The Proceedings of the 1975 Symposium [18] will also be published in English and in Russian and disseminated. Collaborative joint US-USSR projects have been completed or are in progress through the exchange of young U.S. and U.S.S.R. fellows.

Congenital Heart Disease. Congenital heart disease affects an estimated 25,000 children born in the U.S. each year and a corresponding number born in the U.S.S.R. US-USSR collaboration in the field of congenital heart disease was initiated with a joint symposium in 1973 in the U.S.A., and in 1975 a similar joint symposium was held in the U.S.S.R. The proceedings of the first symposium were published in English and in Russian [19], as will those of the second symposium [20]. The topics discussed included the development of diagnostic techniques and methods of postoperative care, study of mechanisms of development of pulmonary hypertension, search for new ways of reducing mortality from surgical treatment of Tetralogy of Fallot (a congenital malfunction of the heart involving four distinct defects), and study of diagnostic techniques and surgical treatment of complex heart defects. Further collaborative activities have included exchange of information and exchange of fellows.

Sudden Death. In order to reduce coronary heart disease mortality, both Soviet and American physicians are searching for effective ways to deal with the problem of sudden death from cardiac arrhythmia. Collaboration on sudden death problems was proposed in 1973. A series of working meetings have been held in the U.S.S.R. between Soviet and American specialists to review the available data on sudden death. The American specialists visited Soviet laboratories working in this field and exchanged information with them on recent studies. An exchange of fellows is planned as are future collaborative projects.

Blood Transfusion, Blood Components, and Prevention of Hepatitis, with Particular Reference to Cardiovascular Surgery. Joint US-USSR efforts in this problem area were established in 1973. They provide for international collaboration in an area of mutual interest, and promote, in each country, the collaboration of internists and surgeons who may view the problems of blood management from different perspectives. Reciprocal visits between Soviet and American scientists during the past year have provided for the exchange of information on important aspects of current transfusion techniques and on blood management practices. Future working meetings have been planned and joint efforts have been organized to improve the technology and practice of blood transfusion in both countries.

Artificial Heart Research and Development. Following two years of exploratory discussions and exchanges, the United States and the Soviet Union, in 1974, signed an agreement designating the field of artificial heart research as a new area of cooperation. The agreement provides for joint efforts in research on, and the development and testing of, devices, materials, instruments, and control mechanisms which will provide cardiovascular support, including total heart replacement. This collaborative program will involve: exchanges of scientific and technical information, organization of joint conferences, workshops, and meetings of experts, exchanges of specialists and delegations, as well as preparation and exchange of different types of circulatory assist devices. A Soviet delegation visited the United States in October 1974 and April 1975 to initiate and develop collaborative efforts in this area.

V. Manpower Development

MANPOWER REQUIREMENTS OF THE NATIONAL PROGRAM

The continued availability of highly qualified manpower is of utmost importance. Trained scientists and their ideas are the source of the new knowledge needed to solve the disease problems now facing the Nation. Recent reports of the NHLBI Advisory Council and of the Institute emphasize strongly the need to develop skilled manpower to replace the continuing losses from the present pool and to supply evolving program needs. It is important to attract able people into biomedical research and to make it possible for the most promising to obtain the best possible education and research experience at pre- and postdoctoral levels, independent of their own personal resources. To maintain a high-quality training environment, it is also necessary for the universities, as well as students, to have sufficient stability to enable them to make sound plans.

The NHLBI has collaborated with a number of professional and private organizations to conduct in-depth assessments of current status and future needs for manpower in the disciplines related to the National Program. The American College of Cardiology, the American Heart Association, the American Association for Thoracic Surgery, the American Thoracic Society, the American College of Chest Physicians, the American Lung Association, the American Society of Hematology, and the American Medical Association have all assisted. The results of these assessments and surveys were reported in the first and second reports of the Director, NHLBI.

Further deficits have resulted from the Institute's increased activities as mandated by the Act. Specific requirements exist for behavioral scientists; basic investigators; population geneticists; protein chemists and immunochemists; investigators with specialized training in endocrinology and metabolism; experts on blood coagulation; blood banking personnel; individuals with expertise in fundamental nutrition, lipid metabolism, growth and development, and pediatrics; epidemiologists; and biostatisticians. Currently there is an exceptional need for nutritionists and epidemiologists to fill vacancies in many of the important new programs which have evolved in response to the 1972 Act. These include the Centers Programs, Clinical Trials Programs, and Prevention, Control, and Education Programs. Descriptions of these programs can be found in Chapter III of this report.

The area of heart and blood vessel diseases has historically been responsible for the largest segment of the NHLBI's training program. Two independent estimates in 1973 [21,22] of research manpower needed to maintain the current trained manpower pool reached essentially the same conclusion: 500 to 600 new investigators are needed each year in the heart and vascular areas alone.

Requirements to overcome an existing shortfall of previous training efforts were estimated at more than 200 faculty positions in 1971 and a total need for more than 1,200 new instructors by 1976 was projected.

The underlying determinants of pulmonary physiology and pathology are being investigated to an increasing extent. Such investigations require training in fundamental disciplines only recently applied to lung research. Therefore, investigators with special, almost unique, requirements are needed to carry out research in pulmonary biochemistry, cell biology, immunology, and bioengineering. To provide the specialized personnel for this research, there is a need for between 150 and 200 research fellows in the immediate future. A 1971 [23] survey of professional manpower needs in lung diseases revealed that 130 currently funded, but unfilled, vacancies exist at research institutes. Taking all the above needs into consideration, approximately 550 well-trained individuals will be required within the next two or three years for these expanded research programs, both basic and clinical, in lung diseases.

In addition to the needs of blood and blood disease research, the rapidly increasing scope of activities in blood banking, and the importance to the Nation's health of an adequate supply of donor blood, requires that well defined training programs be established to fill blood manpower resource needs. Studies conducted in 1971 [24] of hematology staff positions and a survey of blood bank physicians estimated that approximately 20 percent of the funded positions in blood banking research, 10 percent of the positions in hemoglobin research, and 10 percent of the positions in coagulation research were unfilled. On the basis of this survey, it is estimated that approximately 300 training positions per year are necessary to maintain the required pool of hematologists. Trained interdisciplinary manpower for research on thrombosis, biomaterials, and hemoglobin is especially needed.

RESEARCH TRAINING AWARDS OF THE NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

For many years, the National Institutes of Health has had two primary research training awards. One was the Research Fellowship for both pre- and postdoctoral trainees in which the individual applied directly to NIH for a Fellowship Award to receive training at an institution of his choice. The other mechanism was the training grant. Here the training institution received the grant under which it selected its own pre- and postdoctoral fellows and trainees. This mechanism allowed for the development of large, sophisticated, multidisciplinary, and multidepartmental training programs. Each of the three categorical Divisions of the NHLBI has used these training modes to develop manpower resources. The Division of Lung Diseases, because of its unusual manpower needs, developed three additional types of awards.

The National Research Service Award for Individual Postdoctoral Fellows (NRSA). This new award, first made in FY 1975 and used throughout the Institute, supports Postdoctoral Fellows in specified areas of biomedical and behavioral research in which a documented need for trained manpower exists. In FY 1975, 138 such awards were made. The Institute plans to increase Individual Postdoctoral Fellowship Awards to at least 200 awards annually by FY 1978.

The National Research Service Awards for Institutional Research Training (NRSA Institutional). This award is given to eligible institutions to develop or enhance research training opportunities for individuals, selected by the institutions, who are interested in careers in specified areas of biomedical and behavioral research. The Institute employs these institutional awards to foster development of highly trained individuals in the fields where needs are not adequately met by Individual Fellowship Awards. The Institute funded 71 Institutional Research Service Awards during FY 1975; these supported 57 predoctoral and 218 postdoctoral trainees in several areas of acute need. It appears that no new NRSA Institutional Postdoctoral Fellowships may be allowed in FY 1976. This is unfortunate for the Institute perceives an acute need for high quality trainees in several multidisciplinary areas related to Heart, Lung, and Blood Diseases in order to approach established manpower goals.

The National Pulmonary Faculty Training Program. This program includes several interlocking components designed to strengthen pulmonary faculties at schools of medicine and osteopathy and enhance their training environment. Junior faculty members, from schools wishing to strengthen their pulmonary academic programs, can obtain specialized pulmonary training at medical centers where the training environment is supported through the National Faculty Training Program. During FY 1976, the Division of Lung Diseases will invite applications from schools wishing to sponsor junior faculty members for this program.

The Pulmonary Academic Award Program. This program has been employed by the Division of Lung Diseases for several years to provide an impetus for schools of medicine or osteopathy to develop a pulmonary curriculum where none exists, to strengthen and improve curricula which are of limited scope and/or quality, and to stimulate dedicated, well-qualified physician-investigators to devote a major effort to teaching at schools attempting to strengthen their pulmonary programs. Pulmonary Academic Awards are currently supported at 30

institutions where, in most cases, the program has stimulated the development of a pulmonary subspecialty through faculty recruitment, increased input into curriculum planning, and improved status of pulmonary programs. In addition, the program has fostered valuable interchange of ideas and methods within and between participating institutions. In FY 1976, extension of this program to any department wishing to upgrade its pulmonary curriculum is envisioned.

The Young Investigator Pulmonary Research Grant. Young scientists and physicians are awarded this type of grant to carry out a project of their own design in either fundamental or clinical pulmonary research. The Division of Lung Diseases now supports 74 grants under this program.

MINORITY PARTICIPATION IN THE NATIONAL PROGRAM

During the past year, two ad hoc working committees of the National Heart, Lung, and Blood Advisory Council and the National Heart, Lung, and Blood Institute Committee for Minorities have met to formulate and implement programs and activities which will permit individuals and institutions of minority background to:

- Increase and expand their opportunities for participation in National Heart, Lung, and Blood Institute research programs and administration
- Improve communications with National Heart, Lung, and Blood Institute personnel and understand National Heart, Lung, and Blood Institute grant and contract procedures.

A cooperative agreement has been established between the Division of Research Resources (DRR) and the NHLBI to collaborate in the Minority Biomedical Support (MBS) Program administered by DRR. The NHLBI goals in the MBS Program are to:

- Increase the numbers of minority faculty, students, and investigators engaged in biomedical research in the heart, lung, and blood areas
- Broaden the opportunities for participation in biomedical research of minority faculty, students, and investigators
- Assist in the provision of an appropriate setting in which the above two goals can best be accomplished

- Support those aspects of Minority Biomedical Support activities that relate to or have impact on the overall mission of the National Heart, Lung, and Blood Institute

- Provide for a more favorable atmosphere to carry out heart, lung, and blood related research and training through the establishment of essential resources such as animal and equipment centers.

A second cooperative agreement has been arranged between the National Institute of General Medical Sciences (NIGMS) and the NHLBI. NIGMS is accepting applications for Faculty Fellowships under the Minority Access to Research Careers (MARC) Program under the National Research Act (Public Law 93-348). This program is designed to assist minority institutions train greater numbers of health research scientists and teachers. Under the agreement, the three categorical divisions of NHLBI participate in a cooperative effort with the MARC Program.

Recently, the Institute has also embarked on a number of activities to improve communications with ethnic minorities. These have included NHLBI presentations and symposia. Such meetings have provided a useful forum for minority participants to learn about the NHLBI and other NIH programs of interest to them; to establish contacts at NHLBI and elsewhere in NIH; and to seek advice and guidance in the preparation of research proposals. Several such meetings have been held:

- A Minority Research Symposium was held at the Federation of American Societies for Experimental Biology meeting in Atlantic City in April 1975. NHLBI executive staff and 100 minority scientists participated.

- A NHLBI presentation was made at the Macy Foundation Summer Institute for Cell Biologists, Atlanta University, in May 1975. Participants were Ph.D. biology instructors from minority institutions.

- A NHLBI Minority Symposium was conducted in July 1975 at Winston-Salem State University and attended by over 75 science instructors from minority institutions.

VI. Resource Allocations

The National Heart, Blood Vessel, Lung, and Blood Programs deal with problems of great importance to the American people. The efforts expended in this National Program have potential value for every citizen in our country, since the Program deals with diseases that affect all age groups, both men and women, all ethnic groups, and all strata of society. It is estimated that 28,000,000 Americans are afflicted with some form of heart or blood vessel disease: 23,000,000 of them have hypertension; 3,900,000 suffer from coronary heart disease; and 1,700,000 from rheumatic heart disease, while 1,650,000 have had one or more strokes. In 1973, an estimated 1,062,000 Americans died from heart and blood vessel diseases; this represented 53.8 percent of deaths from all causes. These diseases have a profound impact on our nation's economy as well; their annual economic costs are in excess of $57 billion [4].

As in previous reports, the Institute's present resource projections are based on scientific and professional judgement. At the projected level, these should accomplish the Program objectives within the time frame indicated. However, it is recognized that at any given time the allocation of national resources must be determined in relationship to other important competing national priorities. At the present time, the funds available for the implementation of this National Program constitute less than 1 percent of the estimated annual costs to our nation of these diseases.

FISCAL SUMMARY AND PROJECTIONS

In response to the mandates in the National Heart, Blood Vessel, Lung, and Blood Act of 1972, the Institute has initiated activities in a number of new areas. Monitoring and evaluation of ongoing research programs has resulted in identification of expanded opportunities and needs. Recent new research findings have opened potentially new, exciting vistas which require exploration. Research in prevention, control, and education pilot programs has suggested or proven the need for an expansion of NHLBI activities in this area. Also, recent studies have provided a clearer insight into both the manpower and the facilities required for the successful development and timely implementation of the National Program. The opportunities and needs to develop important programs in heart, blood vessel, lung, and blood diseases are at hand, but the ability to do so far exceeds the resources available for the implementation of the National Program.

As a result of the passage of the Act, the Institute has attempted to accelerate important existing programs. Simultaneously, it has moved

vigorously to implement essential new programs included in the National Program Plan. Examples of new activities which have been initiated and which require additional funds and supporting staff include:

- Management and support of large-scale clinical trials in arteriosclerosis, hypertension, myocardial infarction, and coronary artery surgery
- Management and support of the 48 Specialized Centers of Research in arteriosclerosis, hypertension, thrombosis, pulmonary disease, and ischemic heart disease
- Development of new programs in pulmonary diseases and other special new research initiatives
- Development and implementation of Prevention, Control, and Education Programs, as mandated in the Act
- Activities related to the annual updating of the Five-Year National Program Plan, as required by the Act
- Activities related to the development of annual reports by the Director and the Council to the President and Congress, as required by the Act
- Coordination of the National Sickle Cell Disease Program
- Efforts in support of the National Blood Policy
- Establishment of a network of National Research and Demonstration Centers
- Management of interagency activities related to the National Program
- Management of international activities related to the National Program.

To initiate these new programs within the resources available, the Institute has had to severely encroach upon other important program areas of vital importance to the continued success of the National Program. Specifically, it is of concern that due to limited research grant funds, the percentage of investigator-initiated applications, approved for scientific quality and program relevance that have been awarded, has decreased from about 82 percent in FY 1967 to an estimated 52 percent in FY 1975. See Table 5. This table also shows that as the momentum of the National Program increases, more worthy applications are being submitted to the Institute. However,

TABLE 5.
INVESTIGATOR-INITIATED NHLBI GRANT APPLICATION AND AWARD TRENDS

RESEARCH APPLICATION AND AWARD ACTIVITY	1967	1968	1969	1970	1971	1972	1973	1974	1975
Total Number of Applications	1,281	1,210	1,047	1,016	1,107	1,154	1,255	1,463	1,458
Number of Approvals (A)	733	724	615	616	714	735	887	1,084	1,084
Number of Applications Funded (B)	598	474	481	436	431	467	405	573	568
Percentage of Approvals Funded (i.e., B/A x 100)	82	65	78	71	60	62	46	53	52

NHLBI obligations as compared to NIH obligations during the period FY 1967 to FY 1975 remained approximately constant at 16 percent.

The Second Annual Report of the Director, March 10, 1975 [3], contained a detailed fiscal summary and projections for implementing the National Program. These projections are still valid and are summarized below in Tables 6 and 7. The projections in Table 6 were made in the context of the authorizations in the 1972 Act. These were: $375 million for Research and $25 million for Prevention, Control, and Education (PCE) in FY 1973; $425 million for Research and $35 million for PCE in FY 1974; and $425 million for Research and $45 million for PCE in FY 1975.

The resource allocations presented in Table 6 indicate the levels of funding needed to accomplish the objectives defined in the original National Program and Plan which was formulated assuming optimal funds would be available for its execution. The fiscal resources were distributed to build effectively on past accomplishments and to anticipate and exploit future opportunities. However, it is recognized that, at any given time, the allocation of national resources to execute the Institute's Program must be determined in relationship to other national needs. Therefore, an alternative, lowerbound budget resource allocation plan based on new authorization levels is provided in Table 7. This lowerbound budget plan would postpone the funding for certain extramural programs by one or more years as compared to the schedule presented in the initial National Program Plan in May 1973. It would defer the funding of additional National Research and Demonstration Centers until 1979, and limit the number of new centers to three or four. The Prevention, Control, and Education Programs would undergo only modest increases compared to the FY 1976 level in the present budget. Funds for construction would be eliminated, the budget for manpower development would be reduced, and there would be a modest decrease in the intramural research program. The Research Management and Program Services would be adjusted accordingly.

TABLE 6.
PROJECTED RESOURCE ALLOCATIONS* FOR THE NATIONAL HEART, BLOOD VESSEL, LUNG, AND BLOOD PROGRAM FY 77 - FY 81 (DOLLARS IN MILLIONS)

PROGRAM ACTIVITIES	FISCAL YEARS				
	1977	1978	1979	1980	1981
Extramural Research Programs					
Heart and Blood Vessel Diseases	215.4	230.2	244.1	253.3	247.2
Lung Diseases	49.8	53.0	56.0	55.0	54.6
Blood Diseases and Blood Resources	57.9	60.9	63.4	64.2	64.9
National Research and Demonstration Centers	25.3	48.5	55.2	56.7	58.7
Prevention, Control, and Education Programs	29.0	32.5	35.0	38.0	40.0
Construction	60.0	30.0	30.0	0.0	0.0
Manpower	40.7	47.9	48.3	48.4	48.5
Intramural Research Programs	26.0	26.0	26.0	27.0	27.0
Research Management & Program Services	28.1	29.5	31.1	30.2	30.1
TOTAL	$532.2	$558.5	$589.1	$572.8	$571.0

*These tabulations give the primary thrust of activities, even though these activities generally involve more than one subprogram.

TABLE 7.
PROJECTED LOWERBOUND RESOURCE ALLOCATIONS* FOR THE NATIONAL HEART, BLOOD VESSEL, LUNG, AND BLOOD PROGRAM FY 77 - FY 81 (DOLLARS IN MILLIONS)

PROGRAM ACTIVITIES	FISCAL YEARS				
	1977	1978	1979	1980	1981
Extramural Research Programs					
Heart and Blood Vessel Diseases	209.2	215.4	230.2	235.0	240.0
Lung Diseases	47.2	49.8	53.0	54.1	54.6
Blood Diseases and Blood Resources	55.5	57.8	60.8	63.9	64.9
National Research and Demonstration Centers	8.0	8.0	15.0	15.0	15.0
Prevention, Control, and Education Programs	25.0	27.0	30.0	32.0	35.0
Construction	0.0	0.0	0.0	0.0	0.0
Manpower	32.0	32.0	32.5	32.5	33.0
Intramural Research Programs	25.0	26.0	26.0	26.5	26.5
Research Management & Program Services	25.3	26.2	28.2	28.9	29.5
TOTAL	$427.2	$442.2	$475.7	$487.9	$498.5

*These tabulations give the primary thrust of activities, even though these activities generally involve more than one subprogram.

NHLBI STAFF ALLOCATION PLAN

The Act requires that the Plan for the National Program include a statement which sets out the Institute's staff requirements to carry out the Program. The initial Institute plan of May 1973 included such a statement, noting that there were 626 positions authorized for the NHLBI at that time and projecting a need for 810 positions in 1976. This projection to maintain adequate staffing is still valid. Nevertheless, as of June 30, 1975, the authorized ceiling for the Institute is 683 positions.

In response to the Act, the Institute has initiated activity in a number of new areas. Many new programs, especially the many clinical trials and targeted activities, require a high ratio of manpower to dollars. To operate the National Program effectively, the NHLBI needs additional staff, both at the middle and upper professional levels as well as in support positions. Programs such as disease prevention, control, and education, and comprehensive centers are new to the Institute. Their review, administration, and evaluation require new staff with different knowledge and skills than those previously available within the Institute.

From FY 1968 to FY 1975, appropriations increased by 93 percent; that is, nearly doubled, from $168 million in FY 1968 to $324 million in FY 1975. In the same period, the number of positions increased only by 13 percent, from 609 to 691. Despite this small staff increase, several Congressional mandates for important programs were implemented.

Since 1969, the Institute has undergone two name changes. It became the National Heart and Lung Institute in FY 1970 and the National Heart, Lung, and Blood Institute in FY 1976. Passage of the 1972 Act significantly increased Institute responsibilities in heart, lung, and blood diseases. Examples of the Institute's new initiatives which require additional staff are listed under Fiscal Summary and Projections. To initiate these extensive new programs within the available manpower resources, the Institute has conserved manpower in several ways. The Division of Technological Applications was abolished and its activities divided among the three categorical scientific divisions. The review function for programs supported by the grant and contract mechanism were centralized. And, staff was taken from ongoing established programs to meet new program needs. This latter technique has now, however, exhausted all ongoing program flexibility and left the Institute staff perilously overdeployed.

The Institute divisions have formulated plans to implement the Action Items in the National Program Plan. These plans are detailed in the Second Annual Report of the Director, March 10, 1975 [3]. To implement the large number of new initiatives, to keep ongoing programs on target, and to develop these as planned, the Institute urgently needs additional staff to provide for adequate scientific planning, review, coordination, management, and evaluation. These additional positions would allow for improved administration, planning, evaluation, grant and contract administration, and would provide coordination for the Institute's evolving programs in prevention, control, and education. They would also provide additional positions in the intramural and clinical research programs, for scientifically important basic and clinical research programs, in the areas of molecular hematology; kidney, electrolyte, and cell metabolism; and pulmonary diseases.

References

Single copies or information concerning the availability of these publications are available to the public on request from the Information Office, National Heart, Lung, and Blood Institute, Bethesda, Maryland 20014.

[1] The National Heart, Blood Vessel, Lung, and Blood Program Plan was presented in five volumes in May 1973: DHEW Publication Numbers are shown below:

Volume I.	National Heart and Lung Institute Summary (NIH)73-515
Volume II.	Report of the National Heart and Lung Advisory Council (NIH)73-516
Volume III.	Report of the Panel Chairmen (NIH)73-517
Volume IV.	Panel Reports (NIH)73-518 - 73-521
Volume V.	Program Analysis (NIH)73-522 - 73-524

[2] National Heart, Blood Vessel, Lung, and Blood Program, First Annual Report of the Director of the National Heart and Lung Institute, February 13, 1974, DHEW Publication Number (NIH)73-514.

[3] National Heart, Blood Vessel, Lung, and Blood Program, Second Annual Report of the Director of the National Heart and Lung Institute, March 10, 1975, DHEW Publication Number (NIH)75-748.

[4] The Economic Cost of Illness Revisited. Barbara S. Cooper and Dorothy P. Rice, Office of Research and Statistics, Social Security Administration (in preparation), 1975.

[5] Manual of Laboratory Applications, Volume 1, Lipid and Lipoprotein Analysis, DHEW Publication Number (NIH)75-628.

[6] Arteriosclerosis: Report by the National Heart and Lung Institute's Task Force on Arteriosclerosis, Volume I, June 1971, DHEW Publication Number (NIH)72-137.

[7] National Disease and Therapeutic Index (NDTI). IMS America Limited, Ambler, Pennsylvania.

[8] The Proceedings of the First National Symposium on Sickle Cell Disease, June 1974, DHEW Publication Number (NIH)75-723.

[9] Basic Laboratory Methods of Hemoglobinopathy Detection, September 1975, DHEW Publication Number (NIH)76-8266.

[10] Proceedings of the National Heart and Lung Institute Working Conference on Health Behavior, May 12, 1975. DHEW Publication Number (NIH)76-868.

[11] Research Animals in Medicine, 1972, DHEW Publication Number (NIH)73-333, available from the Superintendent of Documents, Government Printing Office, Washington, D.C. 20402. Price is $14.65 per copy.

[12] National Heart, Blood Vessel, Lung, and Blood Program, Volume V, Program Analysis, Parts I, II and III, April 20, 1973. DHEW Publication Numbers (NIH)73-522, 523, and 524.

[13] National Heart, Blood Vessel, Lung, and Blood Program, Related Federally Supported Programs, FY 1973, Parts I and II, May 15, 1974. DHEW Publication Numbers (NIH)75-686 and 687.

[14] National Heart, Blood Vessel, Lung, and Blood Program, Related Federally Supported Programs, FY 1974, Parts I, II and III, November 1975. DHEW Publication Numbers (NIH)76-1001, 1002, and 1003.

[15] Proceedings of the Nutrition-Behavioral Research Conference, April 29, 1975. DHEW Publication Number (NIH)76-978.

[16] Public Law 93-354, National Diabetes Mellitus Research and Education Act, 93rd Congress, S.2830, July 23, 1974.

[17] "US-USSR Symposium on Myocardial Metabolism," Circulation Research, Vol. 35, No. 3, pp. 1-215, September 1974.

[18] "Second Joint US-USSR Symposium on Myocardial Metabolism," to be published, DHEW Publication Number (NIH)76-924.

[19] US-USSR Joint Symposium on Congenital Heart Disease (in English and Russian), 609 p., December 1973, DHEW Publication Number (NIH)74-613.

[20] Second Joint US-USSR Symposium on Congenital Heart Disease (in English) and Russian), to be published in the U.S.S.R.

[21] Manpower Needs in Cardiology, P.L. Frommer, A Memo to the Director, DHVD, NHLI, August 1973.

[22] Position Paper on Manpower Needs, R.S. Ross, P.N. Yu, E. Haber, E. Rapaport, and R. Schneckloth. Communication to Deputy Assistant Secretary for Health, DHEW, May 1973.

[23] Data on Needs for Faculty in U.S. Medical Schools, A Survey. J.F. Hammersten and J.H. Comroe, January 1971.

[24] Survey of Staff Positions in Academic Hematology in 1971, Helen M. Ranney, Louis Kinyon, and Harry A. Sultz, Blood, Vol. 40, No. 4, pp. 574-584, October 1972.

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